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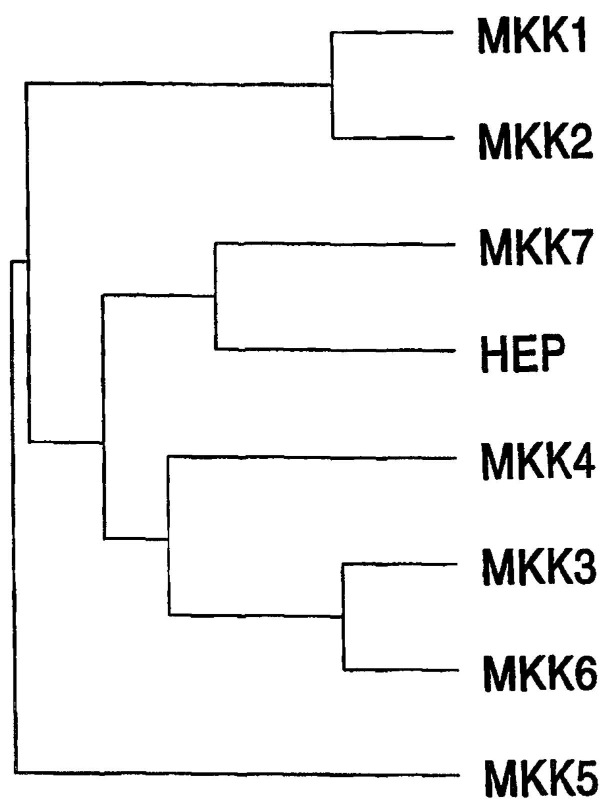
(54) Title: CYTOKINE-, STRESS-, AND ONCOPROTEIN-ACTIVATED HUMAN PROTEIN KINASE KINASES

(57) Abstract

Disclosed are human mitogen-activated (MAP) kinase kinase isoforms (MKKs). MKKs mediate unique signal transduction pathways that activate human MAP kinases p38 and JNK, which result in activation of other factors, including activating transcription factor-2 (ATF2) and c-Jun. The pathways are activated by a number of factors, including cytokines and environmental stress. Methods are provided for identifying reagents that modulate MKK function or activity and for the use of such reagents in the treatment of MKK-mediated disorders.



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CYTOKINE-, STRESS-, AND ONCOPROTEIN-ACTIVATED HUMAN PROTEIN KINASE KINASES

Background of the Invention

This invention relates to protein kinases.

Mitogen-activated protein (MAP) kinases are important mediators of signal transduction from the cell surface to the nucleus. Multiple MAP kinases have been described in yeast including SMK1, HOG1, MPK1, FUS3, and KSS1. In mammals, the MAP kinases identified are extracellular signal-regulated MAP kinase (ERK), c-Jun amino-terminal kinase (JNK), and p38 kinase (Davis (1994) Trends Biochem. Sci. 19:470). These MAP kinase isoforms are activated by dual phosphorylation on threonine and tyrosine.

Activating Transcription Factor-2 (ATF2), ATFa, and cAMP Response Element Binding Protein (CRE-BPa) are related transcription factors that bind to similar sequences located in the promoters of many genes (Ziff (1990) Trends in Genet. 6:69). The binding of these transcription factors leads to increased transcriptional activity. ATF2 binds to several viral proteins, including the oncoprotein E1a (Liu and Green (1994) Nature 368:520), the hepatitis B virus X protein (Maguire et al. (1991) Science 252:842), and the human T cell leukemia virus 1 tax protein (Wagner and Green (1993) Science 262:395). ATF2 also interacts with the tumor suppressor gene product Rb (Kim et al. (1992) Nature 358:331), the high mobility group protein HMG(I)Y (Du et al. (1993) Cell 74:887), and the transcription factors nuclear NF-κB (Du et al. (1993) Cell 74:887) and c-Jun (Benbrook and Jones (1990) Oncogene 5:295).

Summary of the Invention

The invention is based on the identification and isolation of a new group of human mitogen-activated protein kinase kinases (MKKs). The MKK isoforms described herein, MKK3, MKK6, MKK4 (including MKK4-α, -β, and -γ), MKK7 (including murine MKK7, human MKK7, MKK7b, MKK7c, MKK7d, and MKK7e) have serine, threonine, and tyrosine kinase activity. MKK3, MKK4, and MKK6 specifically phosphorylate the human MAP kinase p38 at Thr^{180} and Tyr^{182}. The MKK4 isoforms also phosphorylate the human MAP kinases JNK (including JNK1, JNK2, and JNK5) at Thr^{183} and Tyr^{185}. The MKK7 isoforms phosphorylate JNK at Thr^{183} and Tyr^{185}.

Accordingly, the invention features a substantially pure human MKK polypeptide having serine, threonine, and tyrosine kinase activity that specifically phosphorylates human p38 MAP kinase. MKK3 has the amino acid sequence of SEQ ID NO:2. The invention further includes MKK6 having the amino acid sequence of SEQ ID NO:4 and having serine, threonine, and tyrosine kinase activity that specifically phosphorylates human p38 MAP kinase.

The invention further features a substantially pure human MKK polypeptide having serine, threonine, and tyrosine kinase activity that specifically phosphorylates human p38 MAP kinase and JNK. MKK4 isoform MKK4-α has the amino acid sequence of SEQ ID NO:6. MKK4 isoform MKK4-β has the amino acid sequence of SEQ ID NO:8. MKK4 isoform MKK4-γ has the amino acid sequence of SEQ ID NO:10.

The invention also features a substantially pure MKK polypeptide (MKK7) having serine, threonine, and tyrosine kinase activity that specifically phosphorylates mitogen-activated protein kinase JNK. MKK isoforms MKK7 (murine) and MKK7 (human) have the amino acid sequences

of SEQ ID NOS:18 and 26, respectively. The MKK7 isoforms MKK7b, MKK7c, MKK7d, and MKK7e have the amino acid sequences of SEQ ID NO:20, SEQ ID NO:28, SEQ ID NO:30, and SEQ ID NO:32, respectively.

As used herein, the term "mitogen-activating protein kinase kinase" or "MKK" means a protein kinase which possesses the characteristic activity of phosphorylating and activating a human mitogen-activating protein kinase. Examples of MKKs include MKK3 and MKK6, which specifically phosphorylate and activate p38 MAP kinase at Thr^{180} and Tyr^{182}, MKK4 isoforms which specifically phosphorylate and activate p38 MAP kinase at Thr^{180} and Tyr^{182}, and JNK at Thr^{183} and Tyr^{185}, and MKK7 isoforms which specifically phosphorylate JNK at Thr^{183} and Tyr^{185}.

An "MKK7" is a mammalian isoform of mitogen-activated protein kinase kinase (MKK) polypeptide having serine, threonine, and tyrosine kinase activity, and phosphorylating mitogen-activated protein (MAP) kinase JNK but not p38.

The invention includes the specific p38 and JNK MKKs disclosed, as well as closely related MKKs which are identified and isolated by the use of probes or antibodies prepared from the polynucleotide and amino acid sequences disclosed for the MKKs of the invention. This can be done using standard techniques, e.g., by screening a genomic, cDNA, or combinatorial chemical library with a probe having all or a part of the nucleic acid sequences of the disclosed MKKs. The invention further includes synthetic polynucleotides having all or part of the amino acid sequence of the MKKs herein described.

The term "polypeptide" means any chain of amino acids, regardless of length or post-translational modification (e.g., glycosylation or phosphorylation),

and includes natural proteins as well as synthetic or recombinant polypeptides and peptides.

The term "substantially pure," when referring to a polypeptide, means a polypeptide that is at least 60%, by weight, free from the proteins and naturally-occurring organic molecules with which it is naturally associated. A substantially pure MKK polypeptide (e.g., human) is at least 75%, more preferably at least 90%, and most preferably at least 99%, by weight, MKK polypeptide. A substantially pure MKK can be obtained, for example, by extraction from a natural source; by expression of a recombinant nucleic acid encoding a MKK polypeptide, or by chemically synthesizing the protein. Purity can be measured by any appropriate method, e.g., column chromatography, polyacrylamide gel electrophoresis, or HPLC analysis.

In one aspect, the invention features isolated polynucleotides which encode the MKKs of the invention. In one embodiment, the polynucleotide is the nucleotide sequence of SEQ ID NO:1. In other embodiments, the polynucleotide is the nucleotide sequence of SEQ ID NO:3, SEQ ID NO:5, SEQ ID NO:7, SEQ ID NO:9, SEQ ID NO:17, SEQ ID NO:19, SEQ ID NO:25, SEQ ID NO:27, SEQ ID NO:29, or SEQ ID NO:31, respectively.

As used herein, "polynucleotide" refers to a nucleic acid sequence of deoxyribonucleotides or ribonucleotides in the form of a separate fragment or a component of a larger construct. DNA encoding portions or all of the polypeptides of the invention can be assembled from cDNA fragments or from oligonucleotides that provide a synthetic gene which can be expressed in a recombinant transcriptional unit. Polynucleotide sequences of the invention include DNA, RNA, and cDNA sequences, and can be derived from natural sources or

synthetic sequences synthesized by methods known to the art.

An "isolated" polynucleotide is a nucleic acid molecule that is separated in some way from sequences in the naturally occurring genome of an organism. Thus, the term "isolated polynucleotide" includes any nucleic acid molecules that are not naturally occuring. The term therefore includes, for example, a recombinant polynucleotide which is incorporated into a vector, into an autonomously replicating plasmid or virus, or into the genomic DNA of a prokaryote or eukaryote, or which exists as a separate molecule independent of other sequences. It also includes a recombinant DNA which is part of a hybrid gene encoding additional polypeptide sequences.

The isolated polynucleotide sequences of the invention also include polynucleotide sequences that hybridize under stringent conditions to the polynucleotide sequences specified herein. The term "stringent conditions" means hybridization conditions that guarantee specificity between hybridizing polynucleotide sequences, such as those described herein, or more stringent conditions. One skilled in the art can select posthybridization washing conditions, including temperature and salt concentrations, which reduce the number of nonspecific hybridizations such that only highly complementary sequences are identified (Sambrook et al. (1989) in Molecular Cloning, 2d ed.; Cold Spring Harbor Laboratory Press, Cold Spring Harbor, NY.

The isolated polynucleotide sequences of the invention also include sequences complementary to the polynucleotides encoding MKK (antisense sequences). Antisense nucleic acids are DNA or RNA molecules that are complementary to at least a portion of a specific mRNA molecule (Weintraub (1990) Scientific American 262:40). The invention includes all antisense polynucleotides that

inhibit production of MKK polypeptides. In the cell, the antisense nucleic acids hybridize to the corresponding mRNA, forming a double-stranded molecule. Antisense oligomers of about 15 nucleotides are preferred, since they are easily synthesized and introduced into a target MKK-producing cell. The use of antisense methods to inhibit the translation of genes is known in the art, and is described, e.g., in Marcus-Sakura Anal. Biochem., 172:289 (1988).

In addition, ribozyme nucleotide sequences for MKK are included in the invention. Ribozymes are RNA molecules possessing the ability to specifically cleave other single-stranded RNA in a manner analogous to DNA restriction endonucleases. Through the modification of nucleotide sequences encoding these RNAs, molecules can be engineered to recognize specific nucleotide sequences in an RNA molecule and cleave it (Cech (1988) J. Amer. Med. Assn. 260:3030). A major advantage of this approach is that, because they are sequence-specific, only mRNAs with particular sequences are inactivated.

There are two basic types of ribozymes, *tetrahymena*-type (Hasselhoff (1988) Nature 334:585) and "hammerhead"-type. *Tetrahymena*-type ribozymes recognize sequences which are four bases in length, while "hammerhead"-type ribozymes recognize base sequences 11-18 bases in length. The longer the sequence, the greater the likelihood that the sequence will occur exclusively in the target mRNA species. Consequently, hammerhead-type ribozymes are preferable to *tetrahymena*-type ribozymes for inactivating a specific mRNA species, and 18-base recognition sequences are preferable to shorter recognition sequences.

The MKK polypeptides can also be used to produce antibodies that are immunoreactive or bind epitopes of the MKK polypeptides. Accordingly, one aspect of the

invention features antibodies to the MKK polypeptides of the invention. The antibodies of the invention include polyclonal antibodies which include pooled monoclonal antibodies with different epitopic specificities, as well as distinct monoclonal antibody preparations. Monoclonal antibodies are made from antigen-containing fragments of the MKK polypeptide by methods known in the art (see, for example, Kohler et al. (1975) Nature 256:495).

The term "antibody" as used herein includes intact molecules as well as fragments thereof, such as Fa, $F(ab')_2$, and Fv, which are capable of binding an epitopic determinant. Antibodies that specifically bind MKK polypeptides can be prepared using intact polypeptides or fragments containing small peptides of interest as the immunizing antigen. The polypeptide or peptide used to immunize an animal can be derived from translated cDNA or chemically synthesized, and can be conjugated to a carrier protein, if desired. Commonly used carriers that are chemically coupled to peptides include bovine serum albumin and thyroglobulin. The coupled peptide is then used to immunize the animal (e.g., a mouse, a rat, or a rabbit).

A molecule (e.g., antibody) that "specifically binds" is one that binds to a particular polypeptide, e.g., MKK7, but that does not substantially recoginze or bind to other molecules in a sample, e.g., a biological sample which includes MKK7. References to constructs made of an antibody (or fragment thereof) coupled to a compound comprising a detectable marker include constructs made by any technique, including chemical means and recombinant techniques.

The invention also features methods of identifying subjects at risk for MKK-mediated disorders by measuring activation of the MKK signal transduction pathway. Activation of the MKK signal transduction pathway can be

determined by measuring MKK synthesis; activation of MKK isoforms; activation of MKK substrates p38 or JNK isoforms; or activation of p38 and JNK substrates such as ATF2, ATFa, CRE-BPa, and c-Jun. The term "JNK" or "JNK isoforms" includes JNK1, JNK2, and JNK3. The term "MKK substrate" as used herein includes MKK substrates, as well as MKK substrate substrates, e.g., p38, JNK, ATF2, and c-Jun.

In one embodiment, activation of the MKK signal transduction pathway is determined by measuring activation of the appropriate MKK signal transduction pathway substrates (for example, selected from p38, JNK isoforms, ATF2, ATFa, CRE-BPa, or c-Jun). MKK activity is measured by the rate of substrate phosphorylation as determined by quantitation of the rate of labelled phosphorus (e.g., $[^{32}]P$ or $[^{33}]P$) incorporation. This can also be measured using phosphorylation-specific reagents, such as antibodies. The specificity of MKK substrate phosphorylation can be tested by measuring p38 activation, JNK activation, or both, or by employing mutated p38 or JNK molecules that lack the sites for MKK phosphorylations. Altered phosphorylation of the substrate relative to control values indicates alteration of the MKK signal transduction pathway, and increased risk in a subject of an MKK-mediated disorder. MKK activation of p38 and JNK can be detected in a coupled assay with the MKK signal transduction substrate ATF2, or related compounds such as ATFa and CRE-BPa. Activation can also be detected with the substrate c-Jun. When ATF2 is included in the assay, it is present as an intact protein or as a fragment of the intact protein, e.g., the activation domain (residues 1-109, or a portion thereof). ATF2 is incubated with a test sample in which MKK activity is to be measured and $[\gamma\text{-}^{32}P]ATP$, under conditions sufficient to allow the phosphorylation of

ATF2. ATF2 is then isolated and the amount of phosphorylation quantitated. In a specific embodiment, ATF2 is isolated by immunoprecipitation, resolved by SDS-PAGE, and detected by autoradiography.

In another embodiment, activation of the MKK signal transduction pathway is determined by measuring the level of MKK expression in a test sample. In a specific embodiment, the level of MKK expression is measured by Western blot analysis. The proteins present in a sample are fractionated by gel electrophoresis, transferred to a membrane, and probed with labeled antibodies to MKK. In another specific embodiment, the level of MKK expression is measured by Northern blot analysis. Total cellular or polyadenylated [poly(A)$^+$] mRNA is isolated from a test sample. The RNA is fractionated by electrophoresis and transferred to a membrane. The membrane is probed with labeled MKK cDNA. In another embodiment, MKK expression is measured by quantitative PCR applied to expressed mRNA.

The MKKs of the invention are useful for screening reagents that modulate MKK activity. MKKs are activated by phosphorylation. Accordingly, in one aspect, the invention features methods for identifying a reagent which modulates MKK activity, by incubating MKK with the test reagent and measuring the effect of the test reagent on MKK synthesis, phosphorylation, function, or activity. In one embodiment, the test reagent is incubated with MKK and [^{32}]P-ATP, and the rate of MKK phosphorylation determined, as described above. In another embodiment, the test reagent is incubated with a cell transfected with an MKK polynucleotide expression vector, and the effect of the test reagent on MKK transcription is measured by Northern blot analysis, as described above. In a further embodiment, the effect of the test reagent on MKK synthesis is measured by Western blot analysis

using an antibody to MKK. In still another embodiment, the effect of a reagent on MKK activity is measured by incubating MKK with the test reagent, [^{32}]P-ATP, and a substrate in the MKK signal transduction pathway, including one or more of p38, JNK, and ATF2. The rate of substrate phosphorylation is determined as described above.

The term "modulation of MKK activity" includes inhibitory or stimulatory effects.

The invention is particularly useful for screening reagents that inhibit MKK activity. Such reagents are useful for the treatment or prevention of MKK-mediated disorders, for example, inflammation and oxidative damage.

The invention further features a method of treating a MKK-mediated disorder by administering to a subject in need thereof, an effective dose of a therapeutic reagent that inhibits the activity of MKK.

An "MKK-mediated disorder" is a pathological condition resulting, at least in part, from excessive activation of an MKK signal transduction pathway. The MKK signal transduction pathways are activated by several factors, including inflammation and stress. MKK-mediated disorders include, for example, ischemic heart disease, burns due to heat or radiation (UV, X-ray, γ, β, etc.), kidney failure, liver damage due to oxidative stress or alcohol, respiratory distress syndrome, septic shock, rheumatoid arthritis, autoimmune disorders, and other types of inflammatory diseases.

A "therapeutic reagent" any compound or molecule that achieves the desired effect on an MKK-mediated disorder when administered to a subject in need thereof.

MKK-mediated disorders further include proliferative disorders, particularly disorders that are

stress-related. Examples of stress-related MKK-mediated proliferative disorders are psoriasis, acquired immune deficiency syndrome, malignancies of various tissues of the body, including malignancies of the skin, bone marrow, lung, liver, breast, gastrointestinal system, and genito-urinary tract. Preferably, therapeutic reagents inhibit the activity or expression of MKK inhibit cell growth or cause apoptosis.

A therapeutic reagent that "inhibits MKK activity" interferes with a MKK-mediated signal transduction pathway. For example, a therapeutic reagent can alter the protein kinase activity of MKK, decrease the level of MKK transcription or translation, e.g., an antisense polynucleotide able to bind MKK mRNA, or suppress MKK phosphorylation of p38, JNK, or ATF2, thus disrupting the MKK-mediated signal transduction pathway. Examples of such reagents include antibodies that bind specifically to MKK polypeptides, and fragments of MKK polypeptides that competitively inhibit MKK polypeptide activity.

A therapeutic reagent that "enhances MKK activity" supplements a MKK-mediated signal transduction pathway. Examples of such reagents include the MKK polypeptides themselves, which can be administered in instances where the MKK-mediated disorder is caused by under expression of the MKK polypeptide, or expression of a mutant MKK polypeptide. In addition, portions of DNA encoding an MKK polypeptide can be introduced into cells that under express an MKK polypeptide.

A "therapeutically effective amount" is an amount of a reagent sufficient to decrease or prevent the symptoms associated with the MKK-mediated disorder.

Therapeutic reagents for treatment of MKK-mediated disorders identified by the methods of the invention are administered to a subject in a number of ways known to the art, including parenterally by injection, infusion,

sustained-release injection or implant, intravenously, intraperitoneally, intramuscularly, subcutaneously, or transdermally. Epidermal disorders and disorders of the epithelial tissues are treated by topical application of the reagent. The reagent is mixed with other compounds to improve stability and efficiency of delivery (e.g., liposomes, preservatives, or dimethyl sulfoxide (DMSO)). Polynucleotide sequences, including antisense sequences, can be therapeutically administered by techniques known to the art resulting in introduction into the cells of a subject suffering from the MKK-mediated disorder. These methods include the use of viral vectors (e.g., retrovirus, adenovirus, vaccinia virus, or herpes virus), colloid dispersions, and liposomes.

The materials of the invention are ideally suited for the preparation of a kit for the detection of the level or activity of MKK. Accordingly, the invention features a kit comprising an antibody that binds MKK, or a nucleic acid probe that hybridizes to a MKK polynucleotide, and suitable buffers. The probe or monoclonal antibody can be labeled to detect binding to a MKK polynucleotide or protein. In a preferred embodiment, the kit features a labeled antibody to MKK.

Unless otherwise defined, all technical and scientific terms used herein have the same meaning as commonly understood by one of ordinary skill in the art to which this invention belongs. Although methods and materials similar or equivalent to those described herein can be used in the practice or testing of the present invention, suitable methods and materials are described below. All publications, patent applications, patents, and other references mentioned herein are incorporated by reference in their entirety. In addition, the materials, methods, and examples are illustrative only and not intended to be limiting.

Other features and advantages of the invention will be apparent from the detailed description, and from the claims.

Detailed Description

The drawings will first be described.

Drawings

Fig. 1 is a comparison of the amino acid sequences of MKK3 (SEQ ID NO:2), MKK4-α (SEQ ID NO:6), the human MAP kinase kinases MEK1 (SEQ ID NO:11) and MEK2 (SEQ ID NO:12), and the yeast HOG1 MAP kinase kinase PBS2 (SEQ ID NO:13). Sequences were compared using the PILE-UP program (version 7.2; Wisconsin Genetics Computer Group). The protein sequences are presented in single letter code (A, Ala; C, Cys; D, Asp; E, Glu; F, Phe; G, Gly; H, His; I, Ile; K, Lys; L, Leu; M, Met; N, Asn; P, Pro; Q, Gln; R, Arg; S, Ser; T, Thr; V, Val; W, Trp, and Y, Tyr). The PBS2 sequence is truncated at both the NH_2- (<) and COOH- (>) termini. Gaps introduced into the sequences to optimize the alignment are illustrated by a dash. Identical residues are indicated by a period. The sites of activating phosphorylation in MEK are indicated by asterisks.

Fig. 2A is a dendrogram showing the relationship between members of the human and yeast MAP kinase kinases. The dendrogram was created by the unweighted pair-group method with the use of arithmetic averages (PILE-UP program). The human (hu) MAP kinase kinases MEK1, MEK2, MKK3, and MKK4; the *Saccharomyces cerevisiae* (sc) MAP kinase kinases PBS2, MKK1, and STE7; and the *Saccharomyces pombe* (sp) MAP kinase kinases WIS1 and BYR1 are presented.

Fig. 2B is a dendrogram showing the relationship between MKKs. The dendrogram was created as described for Fig. 2A.

Fig. 3 is a schematic representation of the ERK, p38, and JNK signal transduction pathways. MEK1 and MEK2 are activators of the ERK subgroup of MAP kinase. MKK3 and MKK4 are activators of the p38 MAP kinase. MKK4 is identified as an activator of both the p38 and JNK subgroups of MAP kinase.

Figs. 4A-4D are a representation of the nucleic acid (SEQ ID NO:1) and amino acid sequences (SEQ ID NO:2) for MKK3.

Figs. 5A-5C are a representation of the nucleic acid (SEQ ID NO:3) and amino acid sequences (SEQ ID NO:4) for MKK6.

Figs. 6A-6F are a representation of the nucleic acid (SEQ ID NO:5) and amino acid sequences (SEQ ID NO:6) for MKK4α.

Figs. 7A-7F are a representation of the nucleic acid (SEQ ID NO:7) and amino acid sequences (SEQ ID NO:8) for MKK4β.

Figs. 8A-8F are a representation of the nucleic acid (SEQ ID NO:9) and amino acid sequences (SEQ ID NO:10) for MKK4γ.

Fig. 9 is a representation of the deduced primary structure of MKK7 (SEQ ID NO:18) compared with hep (SEQ ID NO:21), the MAP kinase kinases MEK1 (MKK1; SEQ ID NO:11), MEK2 (MKK2; SEQ ID NO:12), MKK3 (SEQ ID NO:2), MKK4γ (SEQ ID NO:10), MKK5 (SEQ ID NO:22), and MKK6 (SEQ ID NO:4) using the PILE-UP program (version 7,2; Wisconsin Genetics Computer Group). Gaps introduced into the sequences to optimize the alignment are illustrated with a dash (-). Identity is indicated with a dot (.). The sites of activating phosphorylation of MAP kinase kinases (2, 27, 37, and 38) are indicated with asterisks (*).

Figs. 10A-10D are a representation of the nucleic acid (SEQ ID NO:17) and amino acid (SEQ ID NO:18) sequences for MKK7.

Figs. 11A-11D are a representation of the nucleic acid (SEQ ID NO:19) and amino acid (SEQ ID NO:20) sequences of MKK7b.

Figs. 12A-12B are a representation of the nucleic acid (SEQ ID NO:25) and amino acid (SEQ ID NO:26) sequences of human MKK7.

Figs. 13A-13D are a representation of the nucleic acid (SEQ ID NO:27) and amino acid (SEQ ID NO:28) sequences of murine MKK7c.

Figs. 14A-14D are a representation of the nucleic acid (SEQ ID NO:29) and amino acid (SEQ ID NO:30) sequences of murine MKK7d.

Figs. 15A-15D are a representation of the nucleic acid (SEQ ID NO:31) and amino acid (SEQ ID NO:32) sequences of murine MKK7e.

Fig. 16A is a graph of data from a transfection assay in which cells were co-transfected with AP-1 reporter plasmid pTRE-Luciferase with expression vectors for MKK4, MKK7, JNK1, JNK1(APF), or control vector.

Fig. 16B is a graph of a transfection assay in which cells were co-transfected with a GAL4-ATF2 fusion vector and an expression vector for MKK4, MKK7, JNK1, JNK1(APF), or control vector.

Human Mitogen-Activated Protein Kinase Kinases

The human MAP kinase kinases MKK3 and MKK4 (MKK3/4), and MKK7, described herein mediate the transduction of specific signals from the cell surface to the nucleus along specific pathways. These signal transduction pathways are initiated by factors such as cytokines, UV radiation, osmotic shock, and oxidative stress. Activation of MKK3/4, MKK6, and MKK7 results in

activation of the MAP kinases. p38 is activated by MKK3 and MKK4. JNK is activated by MKK4 and MKK7. p38 and JNK in turn activate a group of related transcription factors such as ATF2, ATFa, and CRE-BPa. These transcription factors in turn activate expression of specific genes. For example, ATF2 in known to activate expression of human T cell leukemia virus 1 (Wagner and Green (1993) Science 262:395), transforming growth factor-b2 (Kim et al. (1992) *supra*), interferon-β (Du et al. (1993) Cell 74:887), and E-selectin (DeLuca et al. (1994) J. Biol. Chem. 269:19193). In addition, ATF2 is implicated in the function of a T cell-specific enhancer (Georgopoulos et al. (1992) Mol. Cell. Biol. 12:747).

The JNK group of MAP kinases is activated by exposure of cells to environmental stress or by treatment of cells with pro-inflammatory cytokines (Gupta et al. (1994) EMBO J. 15:2760-2770; Dérijard et al. (1991) Cell 76:1025-1037; Kyriakis et al. (1994) Nature 369:156-160; Sluss et al. (1994) Mol. Cell. Biol. 14:8376-8384; Kallunki et al. (1994) Genes & Dev. 8:2996-3007). Targets of the JNK signal transduction pathway include the transcription factors ATF2 and c-jun (Whitmarsh & Davis (1996) J. Mol. Med. 74:589-607). These transcription factors are members of the bZIP group that bind as homo- and hetero-dimeric complexes to AP-1 and AP-1-like sites in the promoters of many genes (Curran & Franza (1988) Cell 55:395-397). JNK binds to an NH_2-terminal region of ATF2 and c-Jun and phosphorylates two sites within the activation domain of each transcription factor (Dérijard et al. (1994) Cell 76:1025-1037; van Dam et al. (1995) EMBO J. 14:1798-1811; Livingstone et al. (1995) EMBO J. 14:1785-1797). This phosphorylation leads to increased transcriptional activity (Whitmarsh, *supra*). Together, these biochemical studies indicate that the JNK signal transduction pathway contributes to the regulation

of AP-1 transcriptional activity in response to cytokines and environmental stress (Whitmarsh, *supra*). Strong support for this hypothesis is provided by genetic evidence indicating that the JNK signaling pathway is required for the normal regulation of AP-1 transcriptional activity (Yang et al. (1997) Proc. Natl. Acad. Sci. USA, 94:3004-3009).

JNK is activated by dual phosphorylation on Thr-183 and Tyr-185 (Dérijard, *supra*). MKK4 (also known as SEKI) was the first MAP kinase kinase identified as a component of the JNK signal transduction pathway (Dérijard et al. (1995) Science 267:682-685; Lin et al. (1995) Science 268:286-290; Sanchez et al. (1994) Nature 372:794-798). Biochemical studies demonstrate that MKK4 phosphorylates and activates JNK (Dérijard et al. (1995) Science 267:682-685; Lin et al. (1995) Science 268:286-290; Sanchez et al. (1994) Nature 372:794-798). However, the function of MKK4 may not be restricted to the JNK signal transduction pathway because MKK4 also phosphorylates and activates p38 MAP kinase (Dérijard et al. (1995) Science 267:682-685; Lin et al. (1995) Science 268:286-290). This specificity of MKK4 to activate both JNK and p38 MAP kinase provides a mechanism that may account for the co-ordinate activation of these MAP kinases in cells treated with cytokines or environmental stress (Davis (1994) Trends Biochem. Sci. 19:470-473). However, this co-ordinate activation is not always observed. For example, JNK activation in the liver correlates with decreased p38 MAP kinase activity (Mendelson et al. (1996) Proc. Natl. Acad. Sci. USA 93:12908-12913). These data suggest that the properties of MKK4 are insufficient to account for the regulation of JNK in *vivo*.

The isolation of human MKKs is described in Example 1, Example 22, Dérijard et al. ((1995) Science

267:682-685, hereby specifically incorporated by reference), and Raingeaud et al. ((1995) Mol. Cell. Biol. 16:1247-1255). Distinctive regions of the yeast PBS2 sequence were used to design polymerase chain reaction (PCR) primers. Amplification of human brain mRNA with these primers resulted in the formation of specific products which were cloned into a plasmid vector and sequenced. Two different complementary DNAs (cDNAs) that encoded human protein kinases were identified: one encoding a 36 kD protein (MKK3), and one encoding a 44 kD protein (MKK4). MKK4 includes 3 isoforms that vary slightly at the NH_2-terminal, identified as α, β, and γ. The amino acid sequences of MKK3 (SEQ ID NO:2), MKK4-α (SEQ ID NO:6), MKK4-β (SEQ ID NO:8), and MKK4-γ (SEQ ID NO:10) are shown in Fig. 1. The nucleic acid and amino acid sequences of MKK3 (Fig. 4), MKK6 (Fig. 5), MKK4-α (Fig. 6), MKK4-β (Fig. 7), and MKK4-γ (Fig. 8) are also provided. MKK6 was isolated from a human skeletal muscle library by cross-hybridization with MKK3. Except for differences at the N-terminus, MKK6 is highly homologous to MKK3. Other human MKK3 and MKK4 isoforms that exist can be identified by the method described in Example 1.

The expression of these human MKK isoforms was examined by Northern (RNA) blot analysis of mRNA isolated from eight adult human tissues (Example 2). Both protein kinases were found to be widely expressed in human tissues, with the highest expression seen in skeletal muscle tissue.

The substrate specificity of MKK3 was investigated in an *in vitro* phosphorylation assay with recombinant epitope-tagged MAP kinases (JNK1, p38, and ERK2) as substrates (Example 3). MKK3 phosphorylated p38, but did not phosphorylate JNK1 or ERK2. Phosphoaminoacid analysis of p38 demonstrated the presence of a phosphothreonine and phosphotyrosine. Mutational

analysis of p38 demonstrated that replacement of phosphorylation sites Thr^{180} and Tyr^{182} with Ala and Phe, respectively, blocked p38 phosphorylation. These results establish that MKK3 functions *in vitro* as a p38 MAP kinase kinase.

Studies of the *in vitro* substrate specificity of MKK4 are described in Example 4. MKK4 incubated with [γ-^{32}P]ATP, and JNK1, p38, or ERK2 was found to phosphorylate both p38 and JNK1. MKK4 activation of JNK and p38 was also studied by incubating MKK4 with wild-type or mutated JNK1 or p38. The p38 substrate ATF2 was included in each assay. MKK4 was found to exhibit less autophosphorylation than MKK3. MKK4 was also found to be a substrate for activated MAP kinase. Unlike MKK3, MKK4 was also found to activate JNK1. MKK4 incubated with wild-type JNK1, but not mutated JNK1, resulted in increased phosphorylation of ATF2. These results establish that MKK4 is a p38 MAP kinase kinase that also phosphorylates the JNK subgroup of MAP kinases.

In vivo activation of p38 by UV-stimulated MKK3 is described in Example 5. Cells expressing MKK3 were exposed in the presence or absence of UV radiation. MKK3 was isolated by immunoprecipitation and used for protein kinase assays with the substrates p38 or JNK. ATF2 was included in some assays as a substrate for p38 and JNK. MKK3 from non-activated cultured COS cells caused a small amount of phosphorylation of p38 MAP kinase, resulting from basal activity of MKK3. MKK3 from UV-irradiated cells caused increased phosphorylation of p38 MAP kinase, but not of JNK1. An increase in p38 activity was also detected in assays in which ATF2 was included as a substrate. These results establish that MKK3 is activated by UV radiation.

The effect of expression of MKK3 and MKK4 on p38 activity was examined in COS-1 cells (Example 6). Cells

were transfected with a vector encoding p38 and a MEK1, MKK3, or MKK4. Some of the cells were also exposed to EGF or UV radiation. p38 was isolated by immunoprecipitation and assayed for activity with [γ-^{32}P]ATP and ATF2. The expression of the ERK activator MEK1 did not alter p38 phosphorylation of ATF2. In contrast, expression of MKK3 or MKK4 caused increased activity of p38 MAP kinase. The activation of p38 caused by MKK3 and MKK4 was similar to that observed in UV-irradiated cells, and was much greater than that detected in EGF-treated cells. These *in vitro* results provide evidence that MKK3 and MKK4 activate p38 *in vivo*.

A series of experiments was conducted to examine the potential regulation of ATF2 by JNK1. These experiments are described in Gupta et al. (1995) Science 267:389-393, hereby specifically incorporated by reference. The effect of UV radiation on ATF2 phosphorylation was investigated in COS-1 cells transfected with and without epitope-tagged JNK1 (Example 7). Cells were exposed to UV radiation, and JNK1 and JNK2 visualized by in-gel protein kinase assay with the substrate ATF2. JNK1 and JNK2 were detected in transfected and non-transfected cells exposed to UV radiation; however, JNK1 levels were higher in the transfected cells. These results demonstrate that ATF2 is a substrate for the JNK1 and JNK2 protein kinases, and that these protein kinases are activated in cells exposed to UV light.

The site of JNK1 phosphorylation of ATF2 was examined by deletion analysis (Example 8). Progressive NH_2-terminal domain deletion GST-ATF2 fusion proteins were generated, and phosphorylation by JNK1 isolated from UV-irradiated cells was examined. The results showed that JNK1 requires the presence of ATF2 residues 1-60 for phosphorylation of the NH_2-terminal domain of ATF2.

The ATF2 residues required for binding of JNK1 were similarly examined. JNK1 was incubated with immobilized ATF2, unbound JNK1 was removed by extensive washing, and bound JNK1 was detected by incubation with [γ-^{32}P]ATP. Results indicate that residues 20 to 60 of ATF2 are required for binding and phosphorylation by JNK1. A similar binding interaction between ATF2 and the 55 kD JNK2 protein kinase has also been observed.

Phosphorylation by JNK1 was shown to reduce the electrophoretic mobility of ATF2 (Example 9). Phosphoamino acid analysis of the full-length ATF2 molecule (residues 1-505) demonstrated that JNK phosphorylated both Thr and Ser residues. The major sites of Thr and Ser phosphorylation were located in the NH_2 and COOH terminal domains, respectively. The NH_2-terminal sites of phosphorylation were identified as Thr^{69} and Thr^{71} by phosphopeptide mapping and mutational analysis. These sites of Thr phosphorylation are located in a region of ATF2 that is distinct from the sub-domain required for JNK binding (residues 20 to 60).

The reduced electrophoretic mobility seen with phosphorylation of ATF2 was investigated further (Example 10). JNK1 was activated in CHO cells expressing JNK1 by treatment with UV radiation, pro-inflammatory cytokine interleukin-1 (IL-1), or serum. A decreased electrophoretic mobility of JNK1-activated ATF2 was observed in cells treated with UV radiation and IL-1. Smaller effects were seen after treatment of cells with serum. These results indicate that ATF2 is an *in vivo* substrate for JNK1.

The effect of UV radiation on the properties of wild-type ($Thr^{69,71}$) and phosphorylation-defective ($Ala^{69,71}$) ATF2 molecules was investigated (Example 11). Exposure to UV caused a decrease in the electrophoretic mobility of both endogenous and over-expressed wild-type ATF2.

This change in electrophoretic mobility was associated with increased ATF2 phosphorylation. Both the electrophoretic mobility shift and increased phosphorylation were blocked by the replacement of Thr^{69} and Thr^{71} with Ala in ATF2. This mutation also blocked the phosphorylation of ATF2 on Thr residues *in vivo*.

Transcriptional activities of fusion proteins consisting of the GAL4 DNA binding domain and wild-type or mutant ATF2 were examined (Example 12). Point mutations at Thr^{69} and/or Thr^{71} of ATF2 significantly decreased the transcriptional activity of ATF2 relative to the wild-type molecule, indicating the physiological relevance of phosphorylation at these sites for activity.

The binding of JNK1 to the NH_2-terminal activation domain of ATF2 (described in Example 8) suggested that a catalytically inactive JNK1 molecule could function as a dominant inhibitor of the wild-type JNK1 molecule. This hypothesis was investigated by examining the effect of a catalytically inactive JNK1 molecule on ATF2 function (Example 13). A catalytically-inactive JNK1 mutant was constructed by replacing the sites of activating Thr^{183} and Tyr^{185} phosphorylation with Ala and Phe, respectively (Ala^{183},Phe^{185}, termed "dominant-negative"). Expression of wild-type JNK1 caused a small increase in serum-stimulated ATF2 transcriptional activity. In contrast, dominant-negative JNK1 inhibited both control and serum-stimulated ATF2 activity. This inhibitory effect results from the non-productive binding of the JNK1 mutant to the ATF2 activation domain, effectively blocking ATF2 phosphorylation.

The tumor suppressor gene product Rb binds to ATF2 and increases ATF2-stimulated gene expression (Kim et al. (1992) Nature 358:331). Similarly, the adenovirus oncoprotein E1A associates with the DNA binding domain of ATF2 and increases ATF2-stimulated gene expression by a

mechanism that requires the NH_2-terminal activation domain of ATF2 (Liu and Green (1994) Nature 368:520). ATF2 transcriptional activity was investigated with the luciferase reporter gene system in control, Rb-treated, and E1A-treated cells expressing wild-type or mutant ATF2 molecules (Example 14). Rb and E1A were found to increase ATF2-stimulated gene expression of both wild-type and mutant ATF2. However, mutant ATF2 caused a lower level of reporter gene expression than did wild-type ATF2. Together, these results indicate a requirement for ATF2 phosphorylation (on Thr^{69} and Thr^{71}) plus either Rb or E1A for maximal transcriptional activity. Thus, Rb and E1A act in concert with ATF2 phosphorylation to control transcriptional activity.

A series of experiments were conducted to examine the action of p38 activation and to establish the relationship of the p38 MAP kinase pathway to the ERK and JNK signal transduction pathways (Raingeaud et al. (1995) J. Biol. Chem. 270:7420, hereby specifically incorporated by reference). Initially, the substrate specificity of p38 was investigated by incubating p38 with proteins that have been demonstrated to be substrates for the ERK and/or JNK groups of MAP kinases (Example 15). We examined the phosphorylation of MBP (Erickson et al. (1990) J. Biol. Chem. 265:19728), EGF-R (Northwood et al. (1991) J. Biol. Chem. 266:15266), cytoplasmic phospholipase A_2 ($cPLA_2$) (Lin et al. (1993) Cell 72:269), c-Myc (Alvarez et al. (1991) J. Biol. Chem. 266:15277), IκB, c-Jun, and wild-type ($Thr^{69,71}$) or mutated ($Ala^{69,71}$) ATF2. p38 phosphorylated MBP and EGF-R, and to a lesser extent IκB, but not the other ERK substrates, demonstrating that the substrate specificity of p38 differs from both the ERK and JNK groups of MAP kinases. Wild-type ATF2, but not mutated ATF2 ($Ala^{69,71}$), was found to be an excellent p38 substrate.

The phosphorylation of ATF2 by p38 was associated with an electrophoretic mobility shift of ATF2 during polyacrylamide gel electrophoresis. We tested the hypothesis that p38 phosphorylates ATF2 at the same sites as JNK1 by replacing Thr^{69} and Thr^{71} with Ala ($Ala^{69,71}$). It was found that p38 did not phosphorylate mutated ATF2, which demonstrates that p38 phosphorylates ATF2 within the NH_2-terminal activation domain on Thr^{69} and Thr^{71}.

A comparison of the binding of JNK and p38 to ATF2 was conducted by incubating extracts of cells expressing JNK1 or p38 with epitope alone (GST) or GST-ATF2 (residues 1-109 containing the activation domain) (Example 16). Bound protein kinases were detected by Western blot analysis. The results demonstrate that both p38 and JNK bind to the ATF2 activation domain.

EGF and phorbol ester are potent activators of the ERK signal transduction pathway (Egan and Weinberg (1993) Nature 365:781), causing maximal activation of the ERK sub-group of MAP kinases. These treatments, however, cause only a small increase in JNK protein kinase activity (Dérijard et al. (1994) *supra*; Hibi et al. (1993) *supra*). The effects of EGF or phorbol esters, as well UV radiation, osmotic shock, interleukin-1, tumor necrosis factor, and LPS, on p38 activity were all tested (Example 17). Significantly, EGF and phorbol ester caused only a modest increase in p38 protein kinase activity, whereas environmental stress (UV radiation and osmotic shock) caused a marked increase in the activity of both p38 and JNK. Both p38 and JNK were activated in cells treated with pro-inflammatory cytokines (TNF and IL-1) or endotoxic LPS. Together, these results indicate that p38, like JNK, is activated by a stress-induced signal transduction pathway.

ERKs and JNKs are activated by dual phosphorylation within the motifs Thr-Glu-Tyr and Thr-

Pro-Tyr, respectively. In contrast, p38 contains the related sequence Thr-Gly-Tyr. To test whether this motif is relevant to the activation of p38, the effect of the replacement of Thr-Gly-Tyr with Ala-Gly-Phe was examined (Example 18). The effect of UV radiation on cells expressing wild-type (Thr^{180},Tyr^{182}) or mutant p38 (Ala^{180},Phe^{182}) was studied. Western blot analysis using an anti-phosphotyrosine antibody demonstrated that exposure to UV radiation caused an increase in the Tyr phosphorylation of p38. The increased Tyr phosphorylation was confirmed by phosphoamino acid analysis of p38 isolated from [γ-^{32}P]phosphate-labeled cells. This analysis also demonstrated that UV radiation caused increased Thr phosphorylation of p38. Significantly, the increased phosphorylation on Thr^{180} and Tyr^{182} was blocked by the Ala^{180}/Phe^{182} mutation. This result demonstrates that UV radiation causes increased activation of p38 by dual phosphorylation.

It has recently been demonstrated that ERK activity is regulated by the mitogen-induced dual specificity phosphatases MKP1 and PAC1 (Ward et al. (1994) Nature 367:651). The activation of p38 by dual phosphorylation (Example 18) raises the possibility that p38 may also be regulated by dual specificity phosphatases. We examined the effect of MKP1 and PAC1 on p38 MAP kinase activation (Example 19). Cells expressing human MKP1 and PAC1 were treated with and without UV radiation, and p38 activity measured. The expression of PAC1 or MKP1 was found to inhibit p38 activity. The inhibitory effect of MKP1 was greater than PAC1. In contrast, cells transfected with a catalytically inactive mutant phosphatase (mutant PAC1 Cys^{257}/Ser) did not inhibit p38 MAP kinase. These results demonstrate that p38 can be regulated by dual specificity phosphatases PAC1 and MKP1.

The sub-cellular distribution of p38 MAP kinase was examined by indirect immunofluorescence microscopy (Example 20). Epitope-tagged p38 MAP kinase was detected using the M2 monoclonal antibody. Specific staining of cells transfected with epitope-tagged p38 MAP kinase was observed at the cell surface, in the cytoplasm, and in the nucleus. Marked changes in cell surface and nuclear p38 MAP kinase were not observed following UV irradiation, but an increase in the localization of cytoplasmic p38 MAP kinase to the perinuclear region was detected.

A series of experiments were conducted to study the activation of JNK by hyper-osmotic media (Example 21). These experiments were reported by Galcheva-Gargova et al. (1994) Science 265:806, hereby specifically incorporated by reference. CHO cells expressing epitope-tagged JNK1 were incubated with 0 - 1000 mM sorbitol, and JNK1 activity measured in an immune complex kinase assay with the substrate c-Jun. Increased JNK1 activity was observed in cells incubated for 1 hour with 100 mM sorbitol. Increased JNK1 activity was observed within 5 minutes of exposure to 300 mM sorbitol. Maximal activity was observed 15 to 30 minutes after osmotic shock with a progressive decline in JNK1 activity at later times. The activation of JNK by osmotic shock was studied in cells expressing wild-type (Thr^{183}, Tyr^{185}) or mutated (Ala^{183}, Phe^{185}) JNK1. JNK1 activity was measured after incubation for 15 minutes with or without 300 mM sorbitol. Cells expressing wild-type JNK1 showed increased JNK1 activity, while cells expressing mutated JNK1 did not. These results demonstrate that the JNK signal transduction pathway is activated in cultured mammalian cells exposed to hyper-osmotic media.

The results of the above-described experiments are illustrated in Fig. 3, which diagrams the ERK, p38, and

JNK MAP kinase signal transduction pathways. ERKs are potently activated by treatment of cells with EGF or phorbol esters. In contrast, p38 is only slightly activated under these conditions (Example 15). However, UV radiation, osmotic stress, and inflammatory cytokines cause a marked increase in p38 activity. This difference in the pattern of activation of ERK and p38 suggests that these MAP kinases are regulated by different signal transduction pathways. The molecular basis for the separate identity of these signal transduction pathways is established by the demonstration that the MAP kinase kinases that activate ERK (MEK1 and MEK2) and p38 (MKK3, MKK4, and MKK6) are distinct.

The isolation of murine and human MKK7 is described in Example 22. Distinctive regions of the Drosophila MAP kinase kinase *hep* sequence were used to design polymerase chain reaction (PCR) primers. Amplification of murine testis mRNA with these primers resulted in the formation of specific products which were cloned into a plasmid vector and sequenced. One sequence related to *hep* was identified and used to screen a murine testis library. Five DNAs (cDNAs) that encoded protein kinases were identified: one encoding a MAP protein kinase kinase (MKK7). The others encoded various splice variants: MKK7b (a partial sequence appears in Fig. 11), MKK7c (Fig. 13), MKK7d (Fig. 14), MKK7e (Fig. 15). The deduced amino acid sequences of MKK7 (SEQ ID NO:18) and *hep* (SEQ ID NO:21) are shown in Fig. 9, and compared to the MAP kinase kinases MEK1 (SEQ ID NO:11), MEK2 (SEQ ID NO:12), MKK3 (SEQ ID NO:2), MKK4 (SEQ ID NO:10), MKK5 (SEQ ID NO:22), and MKK6 (SEQ ID NO:4). A human MKK7 was identified by screening a human cDNA library with a full-length (mouse) MKK7 cDNA probe. The identified partial sequence (lacking the 3'end) is homologous to mouse MKK7c.

The expression of MKK7 and MKK4 isoforms was examined by Northern (RNA) blot analysis of poly A+ mRNA isolated from eight murine tissues (Example 23). Both protein kinases were found to be widely expressed.

The substrate specificity of MKK7 was investigated in an *in vitro* phosphorylation assay with recombinant, epitope-tagged MAP kinases (JNK1, p38, and ERK2) as substrates (Example 24). MKK7 phosphorylated JNK, but did not phosphorylate p38 or ERK2. MKK7 was phosphorylated by p38 and JNK1.

MKK7 was found to specifically activate JNK protein kinase *in vivo* (Example 25). CHO cells were co-transfected with an epitope-tagged MAP kinase (JNK1, p38, or ERK2) together with an empty expression vector or an expression vector encoding MKK1, MKK4, MKK6, or MKK7 and the product of the phosphorylation reaction analyzed. MKK7 activated only JNK1, and did so to a greater extent than did MKK4.

To test whether MKK7 could cause increased AP-1 transcriptional activity, a co-transfection assay was employed (Example 26). Co-expression of MKK7 with JNK caused an increase in AP-1 reporter gene expression that was greater than the increase seen with MKK4 and JNK. A similar result was seen when ATF2 was used as the reporter gene. In addition, MKK7 alone was able to increase expression of ATF2 (Fig. 16).

MKK isoforms are useful for screening reagents which modulate MKK activity. Described in the Use section following the Examples are methods for identifying reagents capable of inhibiting or activating MKK activity.

The discovery of human MKK isoforms and MKK-mediated signal transduction pathways is clinically significant for the treatment of MKK-mediated disorders. One use of the MKK isoforms is in a method for screening

reagents able to inhibit or prevent the activation of the MKK-MAP kinase- ATF2 pathways.

EXAMPLES

The following examples are meant to illustrate, not limit, the invention.

Example 1. MKK Protein Kinases

The primary sequences of MKK3 and MKK4 were deduced from the sequence of cDNA clones isolated from a human fetal brain library.

The primers TTYTAYGGNGCNTTYTTYATHGA (SEQ ID NO:14) and ATBCTYTCNGGNGCCATKTA (SEQ ID NO:15) were designed based on the sequence of PBS2 (Brewster et al. (1993) Science 259:1760; Maeda et al. (1994) Nature 369:242). The primers were used in a PCR reaction with human brain mRNA as template. Two sequences that encoded fragments of PBS2-related protein kinases were identified. Full-length human cDNA clones were isolated by screening of a human fetal brain library (Dérijard et al. (1995) Science 267:682-685). The cDNA clones were examined by sequencing with an Applied Biosystems model 373A machine. The largest clones obtained for MKK3 (2030 base pairs (bp)) and MKK4 (3576 bp) contained the entire coding region of these protein kinases.

The primary structures of MKK3 (SEQ ID NO:2) and MKK4-α (SEQ ID NO:6) are shown in Fig. 1. An in-frame termination codon is located in the 5′ untranslated region of the MKK3 cDNA, but not in the 5′ region of the MKK4 cDNA. The MKK4 protein sequence presented starts at the second in-frame initiation codon.

These sequences were compared to those of the human MAP kinase kinases MEK1 (SEQ ID NO:11) and MEK2 (SEQ ID NO:12) (Zheng and Guan (1993) J. Biol. Chem 268:11435) and of the yeast MAP kinase kinase PBS2 (SEQ ID NO:13) (Boguslawaski and Polazzi (1987) Proc. Natl.

Acad. Sci. USA 84:5848) (Fig. 1). The identity and similarity of the kinases with human MKK3 (between subdomains I and XI) were calculated with the BESTFIT program (version 7.2; Wisconsin Genetics Computer Group) (percent of identity to percent of similarity): MEK1, 41%/63%; MEK2, 41%/62%; MKK4α, 52%/73%; and PBS2, 40%/59%). The identity and similarity of the kinases with human MKK4α were calculated to be as follows (percent of identity to percent of similarity): MEK1, 44%/63%; MEK2, 45%/61%; MKK3, 52%/73%; and PBS2, 44%/58%.

The cDNA sequences of MKK3 and MKK4γ have been deposited in GenBank with accession numbers L36719 and L36870, respectively. The MKK4γ cDNA sequence contains both the cDNA sequences of MKK4α and MKK4β, which are generated *in vivo* from alternate splicing sites. One of ordinary skill in the art can readily determine the amino acid sequences of MKK3 and MKK4 isoforms from the deposited cDNA sequences.

Example 2. <u>Expression of MKK3 and MKK4 mRNA in Adult Human Tissue</u>

Northern blot analysis was performed with polyadenylated [poly(A)$^+$] mRNA (2 μg) isolated from human heart, brain, placenta, lung, liver, muscle, kidney, and pancreas tissues. The mRNA was fractionated by denaturing agarose gel electrophoresis and was transferred to a nylon membrane. The blot was probed with the MKK3 and MKK4 cDNA labeled by random priming with [α-^{32}P]ATP (deoxyadenosine triphosphate) (Amersham International PLC). MKK3 and MKK4 were expressed in all tissues examined; the highest expression of MKK3 and MKK4 was found in skeletal muscle tissue.

The relation between members of the human and yeast MAP kinase kinase group is presented as a

dendrogram (Fig. 2). MKK3/4 form a unique subgroup of human MAP kinase kinases.

Example 3. *In Vitro* Phosphorylation of p38 MAP kinase by MKK3

GST-JNK1, and GST-ERK2 have been described (Dérijard et al. (1994) *supra*; Gupta et al. (1995) Science 267:389; Wartmann and Davis (1994) J. Biol. Chem. 269:6695, each herein specifically incorporated by reference). GST-p38 MAP kinase was prepared from the expression vector pGSTag (Dressier et al. (1992) Biotechniques 13:866) and a PCR fragment containing the coding region of the p38 MAP kinase cDNA. GST-MKK3 and MKK4 were prepared with pGEX3X (Pharmacia-LKB Biotechnology) and PCR fragments containing the coding region of the MKK3 and MKK4 cDNAs. The GST fusion proteins were purified by affinity chromatography with the use of GSH-agarose (Smith and Johnson (1988) Gene 67:31). The expression vectors pCMV-Flag-JNK1 and pCMV-MEK1 have been described (Dérijard et al. (1994) *supra*; Wartmann and Davis (1994) *supra*). The plasmid pCMV-Flag-p38 MAP kinase was prepared with the expression vector pCMV5 (Andersson et al. (1989) J. Biol. Chem. 264:8222) and the p38 MAP kinase cDNA. The expression vectors for MKK3 and MKK4 were prepared by subcloning of the cDNAs into the polylinker of pCDNA3 (Invitrogen). The Flag epitope (Asp-Tyr-Lys-Asp-Asp-Asp-Asp-Lys (SEQ ID NO:16); Immunex, Seattle, WA) was inserted between codons 1 and 2 of the kinases by insertional overlapping PCR (Ho et al. (1989) Gene 77:51).

Protein kinase assays were performed in kinase buffer (25 mM 4-(2-hydroxyethyl)-1-piperazineethansulfonic acid, pH 7.4, 25 mM β-glycerophosphate, 25 mM $MgCl_2$, 2 mM dithiothreitol, and 0.1 mM orthovanadate). Recombinant GST-MKK3 was

incubated with [γ-^{32}P]ATP and buffer, GST-JNK1, GST-p38 MAP kinase, or GST-ERK2. The assays were initiated by the addition of 1 μg of substrate proteins and 50 μM [γ-^{32}P]ATP (10 Ci/mmol) in a final volume of 25 μl. The reactions were terminated after 30 minutes at 25°C by addition of Laemmli sample buffer. The phosphorylation of the substrate proteins was examined after SDS-polyacrylamide gel electrophoresis (SDS-PAGE) by autoradiography. Phosphoaminoacid analysis was performed by partial acid hydrolysis and thin-layer chromatography (Dérijard et al. (1994) *supra*; Alvarez et al. (1991) J. Biol. Chem. 266:15277). Autophosphorylation of MKK3 was observed in all groups. MKK3 phosphorylated p38 MAP kinase, but not JNK1 or ERK2.

A similar insertional overlapping PCR procedure was used to replace Thr^{180} and Tyr^{182} of p38, with Ala and Phe, respectively. The sequence of all plasmids was confirmed by automated sequencing on an Applied Biosystems model 373A machine. GST-MKK3 was incubated with [γ-^{32}P]ATP and buffer, wild-type GST-p38 MAP kinase (TGY), or mutated GST-p38 MAP kinase (AGF). The phosphorylated proteins were resolved by SDS-PAGE and detected by autoradiography. Only phosphorylation of wild-type p38 was observed.

Example 4. *In Vitro* Phosphorylation and Activation of JNK and p38 MAP Kinase by MKK4

Protein kinase assays were conducted as described in Example 3. Recombinant GST-MKK4 was incubated with [γ-^{32}P]ATP and buffer, GST-JNK1, GST-p38 MAP kinase, or GST-ERK2. JNK1 and p38 were phosphorylated, as was MKK4 incubated with JNK1 and p38.

GST-MKK4 was incubated with [γ-^{32}P]ATP and buffer, wild-type JNK1 (Thr^{183}, Tyr^{185}), or mutated GST-JNK1 (Ala^{183}, Phe^{185}). The JNK1 substrate ATF2 (Gupta et al. (1995)

supra) was included in each incubation. ATF2 was phosphorylated in the presence of MKK4 and wild-type JNK1. The results establish that MKK4 phosphorylates and activates both p38 and JNK1.

Example 5. <u>Phosphorylation and Activation of p38 MAP Kinase by UV-stimulated MKK3</u>

Epitope-tagged MKK3 was expressed in COS-1 cells maintained in Dulbecco's modified Eagle's medium supplemented with fetal bovine serum (5%)(Gibco-BRL). The cells were transfected with the lipofectamine reagent according to the manufacturer's recommendations (Gibco-BRL) and treated with UV radiation or EGF as described (Dérijard et al. (1994) *supra*).

The cells were exposed in the absence and presence of UV-C (40 J/m^2). The cells were solubilized with lysis buffer (20 mM tris, pH 7.4, 1% TRITON® X-100, 10% glycerol, 137 mM NaCl, 2 mM EDTA, 25 mM β-glycerophosphate, 1 mM Na orthovanadate, 1 mM phenylmethylsulfonyl fluoride, and leupeptin (10 μg/ml)) and centrifuged at 100,000 x g for 15 minutes at 4°C. MKK3 was isolated by immunoprecipitation. The epitope-tagged protein kinases were incubated for 1 hour at 4°C with the M2 antibody to the Flag epitope (IBI-Kodak) bound to protein G-Sepharose (Pharmacia-LKB Biotechnology). The immunoprecipitates were washed twice with lysis buffer and twice with kinase buffer.

Protein kinase assays were conducted with the substrate GST-p38 MAP kinase or JNK1. ATF2 was included in some assays. Basal levels of MKK3 phosphorylation of p38 MAP kinase were observed. UV-irradiation resulted in increased phosphorylation of p38 MAP kinase, but not of JNK1. The increased p38 MAP kinase activity resulted in increased phosphorylation of ATF2.

Example 6. Activation of p38 MAP Kinase in Cells Expressing MKK3 and MKK4

COS-1 cells were transfected with epitope-tagged p38 MAP kinase, together with an empty expression vector or an expression vector encoding MEK1, MKK3, or MKK4α. Some of the cultures were exposed to UV radiation (40 J/m^2) or treated with 10 nM EGF. p38 MAP kinase was isolated by immunoprecipitation with M2 monoclonal antibody, and the protein kinase activity was measured in the immunecomplex with [γ-^{32}P]ATP and ATF2 as substrates. The product of the phosphorylation reaction was visualized after SDS-PAGE by autoradiography. ATF2 was not phosphorylated in the control MEK1, or EGF-treated groups, but was phosphorylated in the MKK3, MKK4, and UV-irradiated groups. MKK3 and MKK4 phosphorylation of ATF2 was similar to that seen with p38 MAP kinase isolated from UV-irradiated cells.

Example 7. Phosphorylation of ATF2 by JNK1 and JNK2

COS-1 cells were maintained in Dulbecco's modified Eagle's medium supplemented with bovine serum albumin (5%) (Gibco-BRL). Metabolic labeling with [^{32}]P was performed by incubation of cells for 3 hours in phosphate-free modified Eagle's medium (Flow Laboratories Inc.) supplemented with [^{32}P]orthophosphate (2 mCi/ml) (Dupont-NEN). COS-1 cells were transfected without (Mock) and with epitope-tagged JNK1 (JNK1). Plasmid expression vectors encoding the JNK1 cDNA have previously been described (Dérijard et al. (1994) Cell 76:1025, herein specifically incorporated by reference). Plasmid DNA was transfected into COS-1 cells by the lipofectamine method (Gibco-BRL). After 48 hours of incubation, some cultures were exposed to 40 J/m^2 UV radiation and incubated for 1 hour at 37°C.

Cells were lysed in 20 mM Tris, pH 7.5, 25 mM β-glycerophosphate, 10% glycerol, 1% Triton® X-100, 0.5% (w/v) deoxycholate, 0.1% (w/v) SDS, 0.137 M NaCl, 2 mM pyrophosphate, 1 mM orthovanadate, 2 mM EDTA, 10 μg/ml leupeptin, 1 mM PMSF. Soluble extracts were prepared by centrifugation in a microfuge for 20 minutes at 4°C. JNK1 immunoprecipitates were also prepared by reaction with a rabbit antiserum prepared with recombinant JNK1 as an antigen.

In-gel protein kinase assays were performed with cell lysates and JNK1 immunoprecipitates after SDS-PAGE by renaturation of protein kinases, polymerization of the substrate (GST-ATF2, residues 1-505) in the gel, and incubation with [γ-^{32}P]ATP (Dérijard et al. (1994) *supra*). The incorporation of [^{32}P]phosphate was visualized by autoradiography and quantitated with a Phosphorimager and ImageQuant software (Molecular Dynamics Inc., Sunnyvale, CA). The cell lysates demonstrate the presence of 46 kD and 55 kD protein kinases that phosphorylate ATF2 in extracts prepared from UV-irradiated cells. The 46 kD and 55 kD protein kinases were identified as JNK1 and JNK2, respectively.

Example 8. <u>Binding of JNK1 to ATF2 and Phosphorylation of the NH_2-Terminal Activation Domain</u>

The site of JNK1 phosphorylation of ATF2 was investigated by generation of progressive NH_2-terminal domain deletions of ATF2. Plasmid expression vectors encoding ATF2 (pECE-ATF2) (Liu and Green (1994) and (1990)), have been described. Bacterial expression vectors for GST-ATF2 fusion proteins were constructed by sub-cloning ATF2 cDNA fragments from a polymerase chain reaction (PCR) into pGEX-3X (Pharmacia-LKB Biotechnology Inc.). The sequence of all constructed plasmids was confirmed by automated sequencing with an Applied

Biosystems model 373A machine. The GST-ATF2 proteins were purified as described (Smith and Johnson (1988) Gene 67:31), resolved by SDS-PAGE and stained with Coomassie blue. GST-ATF2 fusion proteins contained residues 1-505, 1-349, 350-505, 1-109, 20-109, 40-109, and 60-109.

The phosphorylation of GST-ATF2 fusion proteins by JNK1 isolated from UV-irradiated cells was examined in an immunocomplex kinase assay. Immunecomplex kinase assays were performed with Flag epitope-tagged JNK1 and the monoclonal antibody M2 (IBI-Kodak) as described by Dérijard et al. (1994) *supra*). Immunecomplex protein kinase assays were also performed with a rabbit antiserum prepared with recombinant JNK1 as an antigen. The cells were solubilized with 20 mM Tris, pH 7.5, 10% glycerol, 1% Triton® X-100, 0.137 M NaCl, 25 mM β-glycerophosphate, 2 mM EDTA, 1 mM orthovanadate, 2 mM pyrophosphate, 10 μg/ml leupeptin, and 1 mM PMSF. JNK1 was immunoprecipitated with protein G-Sepharose bound to a rabbit polyclonal antibody to JNK or the M2 monoclonal antibody to the Flag epitope. The beads were washed three times with lysis buffer and once with kinase buffer (20 mM Hepes, pH 7.6, 20 mM $MgCl_2$, 25 mM β-glycerophosphate, 100 μM Na orthovanadate, 2 mM dithiothreitol). The kinase assays were performed at 25°C for 10 minutes with 1 μg of substrate, 20 μM adenosine triphosphate and 10 μCi of [γ-^{32}P]ATP in 30μl of kinase buffer. The reactions were terminated with Laemmli sample buffer and the products were resolved by SDS-PAGE (10% gel). JNK1 phosphorylates GST-ATF2 fusion proteins containing residues 1-505, 1-349, 1-109, 20-109, and 40-109, but not 60-109. These results indicate that the presence of ATF2 residues 1-60 are required for phosphorylation by JNK.

The binding of immobilized GST-ATF2 fusion proteins was examined in a solid-phase kinase assay as

described by Hibi et al. ((1993) Genes Dev. 7:2135, herein specifically incorporated by reference). JNK1 from UV-irradiated cells was incubated with GST-ATF2 fusion proteins bound to GSH-agarose. The agarose beads were washed extensively to remove the unbound JNK1. Phosphorylation of the GST-ATF2 fusion proteins by the bound JNK1 protein kinase was examined by addition of [γ-^{32}P]ATP. JNK1 bound GST-ATF2 fusion proteins containing residues 1-505, 1-349, 1-109, 20-109, and 40-109, indicating that the presence of residues 20-60 were required for binding of JNK1 to ATF2.

Example 9. <u>Phosphorylation of the NH_2-terminal Activation Domain of ATF2 on Thr^{69} and Thr^{71} by JNK1</u>

The effect of UV radiation on the properties of wild-type ($Thr^{69,71}$) and phosphorylation-defective ($Ala^{69,71}$) ATF2 molecules was examined. Mock-transfected and JNK1-transfected COS cells were treated without and with 40 J/m^2 UV radiation. The epitope-tagged JNK1 was isolated by immunoprecipitation with the M2 monoclonal antibody. The phosphorylation of GST-ATF2 (residues 1 to 109) was examined in an immunocomplex kinase assay as described above. The GST-ATF2 was resolved from other proteins by SDS-PAGE and stained with Coomassie blue. The phosphorylation of GST-ATF2 was detected by autoradiography. JNK1-transfected cells, but not mock-transfected cells, phosphorylated ATF2. JNK1 phosphorylation of ATF2 was greater in cells exposed to UV radiation. Phosphorylation of ATF2 by JNK1 was associated with a decreased electrophoretic mobility.

In a separate experiment, GST fusion proteins containing full-length ATF2 (residues 1 to 505), an NH_2-terminal fragment (residues 1 to 109), and a COOH-terminal fragment (residues 95 to 505) were

phosphorylated with JNK1 and the sites of phosphorylation analyzed by phosphoamino acid analysis. The methods used for phosphopeptide mapping and phosphoamino acid analysis have been described (Alvarez et al. (1991) J. Biol. Chem. 266:15277). The horizontal dimension of the peptide maps was electrophoresis and the vertical dimension was chromatography. The NH_2-terminal sites of phosphorylation were identified as Thr^{69} and Thr^{71} by phosphopeptide mapping and mutational analysis. Site-directed mutagenesis was performed as described above, replacing Thr^{69} and Thr^{71} with Ala. Phosphorylation of mutated ATF2 was not observed.

Example 10. Reduced Electrophoretic Mobility of JNK-Activated ATF2

CHO cells were maintained in Ham's F12 medium supplemented with 5% bovine serum albumin (Gibco-BRL). Cells were labeled and transfected with JNK1 as described above. CHO cells were treated with UV-C (40 J/m^2), IL-1α (10 ng/ml) (Genzyme), or fetal bovine serum (20%) (Gibco-BRL). The cells were incubated for 30 minutes at 37oC prior to harvesting. The electrophoretic mobility of ATF2 after SDS-PAGE was examined by protein immuno-blot analysis. A shift in ATF2 electrophoretic mobility was observed in cells treated with UV, IL-1, and serum. These results indicate that JNK1 activation is associated with an electrophoretic mobility shift of ATF2, further suggesting that ATF2 is an *in vivo* substrate for JNK1.

Example 11. Increased ATF2 Phosphorylation After Activation of JNK

COS-1 cells were transfected without (control) and with an ATF2 expression vector (ATF2), as described above (Hai et al. (1989) *supra*). The effect of exposure of the cells to 40 J/m^2 UV-C was examined. After irradiation,

the cells were incubated for 0 or 30 minutes (control) or 0, 15, 30, and 45 minutes (ATF2) at 37oC and then collected. The electrophoretic mobility of ATF2 during SDS-PAGE was examined by protein immuno-blot analysis as described above. The two electrophoretic mobility forms of ATF2 were observed in ATF2-transfected cells, but not in control cells.

The phosphorylation state of wild-type ($Thr^{69,71}$) ATF2 and mutated ($Ala^{69,71}$) ATF2 was examined in cells labeled with [^{32}]P, treated without and with 40 J/m^2 UV-C, and then incubated at 37oC for 30 minutes (Hai et al. (1989) *supra*). The ATF2 proteins were isolated by immunoprecipitation and analyzed by SDS-PAGE and autoradiography. The phosphorylated ATF2 proteins were examined by phosphoamino acid analysis as described above. Both forms of ATF2 contained phosphoserine, but only wild-type ATF2 contained phosphothreonine.

Tryptic phosphopeptide mapping was used to compare ATF2 phosphorylated *in vitro* by JNK1 with ATF2 phosphorylated in COS-1 cells. A map was also prepared with a sample composed of equal amounts of *in vivo* and *in vitro* phosphorylated ATF2 (Mix). Mutation of ATF2 at Thr^{69} and Thr^{71} resulted in the loss of two tryptic phosphopeptides in maps of ATF2 isolated from UV-irradiated cells. These phosphopeptides correspond to mono- and bis-phosphorylated peptides containing Thr^{69} and Thr^{71}. Both of these phosphopeptides were found in maps of ATF2 phosphorylated by JNK1 *in vitro*.

Example 12. Inhibition of ATF2-Stimulated Gene Expression by Mutation of the Phosphorylation Sites Thr^{69} and Thr^{71}

A fusion protein consisting of ATF2 and the GAL4 DNA binding domain was expressed in CHO cells as described above. The activity of the GAL4-ATF2 fusion

protein was measured in co-transfection assays with the reporter plasmid pG5E1bLuc (Seth et al. (1992) J. Biol. Chem. 267:24796, hereby specifically incorporated by reference). The reporter plasmid contains five GAL4 sites cloned upstream of a minimal promoter element and the firefly luciferase gene. Transfection efficiency was monitored with a control plasmid that expresses β-galactosidase (pCH110; Pharmacia-LKB Biotechnology). The luciferase and β-galactosidase activity detected in cell extracts was measured as the mean activity ratio of three experiments (Gupta et al. (1993) Proc. Natl. Acad. Sci. USA 90:3216, hereby specifically incorporated by reference). The results, shown in Table 1, demonstrate the importance of phosphorylation at Thr^{69} and Thr^{71} for transcriptional activity.

TABLE 1. INHIBITION OF ATF-2 STIMULATED GENE EXPRESSION BY MUTATION OF THE PHOSPHORYLATION SITES $THR^{69,71}$

PROTEIN	LUCIFERASE ACTIVITY (Light Units/OD)
GAL4	45
GAL4-ATF2 (wild type)	320,000
GAL4-ATF2 (Ala^{69})	24,000
GAL4-ATF2 (Ala^{71})	22,000
GAL4-ATF2 ($Ala^{69,71}$)	29,000
GAL4-ATF2 (Glu^{69})	27,000

Example 13. <u>Effect of Dominant-Negative JNK1 Mutant on ATF2 Function</u>

The luciferase reporter plasmid system was used to determine the effect of point mutations at the ATF2 phosphorylation sites Thr^{69} and Thr^{71} in serum-treated CHO cells transfected with wild-type (Thr^{183}, Tyr^{185}) or mutant (Ala^{183}, Phe^{185}) JNK1. Control experiments were done with mock-transfected cells. The CHO cells were serum-starved

for 18 hours and then incubated without or with serum for 4 hours. Expression of wild-type ATF2 caused a small increase in serum-stimulated ATF2 transcriptional activity. In contrast, mutant JNK1 inhibited both control and serum-stimulated ATF2 activity.

Example 14. Effect of Tumor Suppressor Gene Product Rb and Adenovirus Oncoprotein E1A on ATF2-Stimulated Gene Expression

The effect of expression of the Rb tumor suppressor gene product and adenovirus oncoprotein E1A on ATF2 transcriptional activity were investigated with a luciferase reporter plasmid and GAL4-ATF2 (residues 1-505), as described above. Cells were transfected with wild-type ($Thr^{69,71}$) or mutated ($Ala^{69,71}$) ATF2. No effect of Rb or E1A on luciferase activity was detected in the absence of GAL4-ATF2. Rb and E1A were found to increase ATF2-stimulated gene expression of both wild-type and mutated ATF2. However, mutated ATF2 caused a lower level of reporter gene expression than did wild-type ATF2. These results indicate a requirement for ATF2 phosphorylation (on Thr^{69} and Thr^{71}) plus either Rb or E1A for maximal transcriptional activity.

Example 15. Substrate Specificity of p38 MAP Kinase

Substrate phosphorylation by p38 MAP kinase was examined by incubation of bacterially-expressed p38 MAP kinase with IκB, cMyc, EGF-R, cytoplasmic phospholipase A_2 ($cPLA_2$), c-Jun, and mutated ATF2 ($Thr^{69,71}$) and ATP[γ-^{32}P] (Raingeaud et al. (1995) J. Biol. Chem 270:7420, herein specifically incorporated by reference). GST-IκB was provided by Dr D. Baltimore (Massachusetts Institute of Technology). GST-cMyc (Alvarez et al. (1991) J. Biol. Chem. 266:15277), GST-EGF-R (residues 647-688) (Koland et al. (1990) Biochem. Biophys. Res. Commun. 166:90), and GST-c-Jun (Dérijard et al. (1994) *supra*) have been

described. The phosphorylation reaction was terminated after 30 minutes by addition of Laemmli sample buffer. The phosphorylated proteins were resolved by SDS-PAGE and detected by autoradiography. The rate phosphorylation of the substrate proteins was quantitated by PhosphorImager (Molecular Dynamics Inc.) analysis. The relative phosphorylation of ATF2, MBP, EGF-R, and IκB was 1.0, 0.23, 0.04, and 0.001, respectively.

Example 16. Binding of p38 MAP Kinase to ATF2

Cell extracts expressing epitope-tagged JNK1 and p38 MAP kinase were incubated with a GST fusion protein containing the activation domain of ATF2 (residues 1-109) immobilized on GSH agarose. The supernatant was removed and the agarose was washed extensively. Western blot analysis of the supernatant and agarose-bound fractions was conducted as follows: proteins were fractionated by SDS-PAGE, electrophoretically transferred to an Immobilon-P membrane, and probed with monoclonal antibodies to phosphotyrosine (PY20) and the Flag epitope (M2). Immunocomplexes were detected using enhanced chemiluminescence (Amersham International PLC). Control experiments were performed using immobilized GST.

Example 17. p38 MAP Kinase and JNK1 Activation by Pro-Inflammatory Cytokines and Environmental Stress

The effect of phorbol ester, EGF, UV radiation, osmotic stress, IL-1, tumor necrosis factor (TNF), and LPS on p38 MAP kinase and JNK1 activity were measured in immunecomplex protein kinase assays using ATP[γ-^{32}P] and ATF2 as substrates. TNFα and IL-1α were from Genzyme Corp. Lipolysaccharide (LPS) was isolated from lyophilized *Salmonella minesota* Re595 bacteria as described (Mathison et a. (1988) J. Clin. Invest.

81:1925). Phorbol myristate acetate was from Sigma. EGF was purified from mouse salivary glands (Davis (1988) J. Biol. Chem. 263:9462). Kinase assays were performed using immunoprecipitates of p38 and JNK. The immunocomplexes were washed twice with kinase buffer (described above), and the assays initiated by the addition of 1 μg of ATF2 and 50 μM [γ-^{32}P]ATP (10 Ci/mmol) in a final volume of 25 μl. The reactions were terminated after 30 minutes at 30°C by addition of Laemmli sample buffer. The phosphorylation of ATF2 was examined after SDS-PAGE by autoradiography, and the rate of ATF2 phosphorylation quantitated by PhosphorImager analysis.

The results are shown in Table 2. Exposure of HeLa cells to 10 nM phorbol myristate acetate very weakly activated p38 and JNK1. Similarly, treatment with 10 nM EGF only weakly activated p38 and JNK1. By contrast, treatment with 40 J/m^2 UV-C, 300 mM sorbitol, 10 ng/ml interleukin-1, and 10 ng/ml TNFα strongly activated p38 and JNK1 activity. The effect of LPS on the activity of p38 was examined using CHO cells that express human CD14. Exposure of CHO cells to 10 ng/ml LPS only slightly activated p38 and JNK1 activity.

TABLE 2. p38 AND JNK1 ACTIVATION BY PRO-INFLAMMATORY CYTOKINES AND ENVIRONMENTAL STRESS.

	Relative Protein Kinase Activity JNK	p38
Control	1.0	1.0
Epidermal Growth Factor (10 nM)	1.9	2.1
Phorbol Ester (10 nM)	2.3	2.9
Lipopolysaccharide (10 ng/ml)	3.6	3.7
Osmotic Shock (300 mM sorbitol)	18.1	4.2
Tumor Necrosis Factor (10 ng/ml)	19.3	10.3
Interleukin-1 (10 ng/ml)	8.9	6.2
UV (40 J/m^2)	7.4	17.1

Example 18. p38 MAP Kinase Activation by Dual Phosphorylation on Tyr and Thr

COS-1 cells expressing wild-type (Thr^{180}, Tyr^{182}) or mutated (Ala^{180}, Phe^{182}) p38 MAP kinase were treated without and with UV-C (40 J/m^2). The cells were harvested 30 minutes following exposure with or without UV radiation. Control experiments were performed using mock-transfected cells. The level of expression of epitope-tagged p38 MAP kinase and the state of Tyr phosphorylation of p38 MAP kinase was examined by Western blot analysis using the M2 monoclonal antibody and the phosphotyrosine monoclonal antibody PY20. Immune complexes were detected by enhanced chemiluminescence.

Wild-type and mutant p38 were expressed at similar levels. Western blot analysis showed that UV radiation caused an increase in the Tyr phosphorylation of p38. The increased Tyr phosphorylation was confirmed by phosphoamino acid analysis of p38 isolated from [^{32}P]phosphate-labeled cells. The results also showed that UV radiation increased Thr phosphorylation of p38. The increased phosphorylation on Tyr and Thr was blocked by mutated p38. Wild-type and mutated p38 were isolated from the COS-1 cells by immunoprecipitation. Protein kinase activity was measured in the immune complex using [γ-^{32}P]ATP and GST-ATF2 as substrates. The phosphorylated GST-ATF2 was detected after SDS-PAGE by autoradiography. UV radiation resulted in a marked increase in the activity of wild-type p38, while the mutant p38 was found to be catalytically inactive. These results show that p38 is activated by dual phosphorylation within the Thr-Gly-Tyr motif.

Example 19. MAP Kinase Phosphatase Inhibits p38 MAP kinase Activation

The cells were treated without and with 40 J/m^2 UV-C. Control experiments were performed using mock-transfected cells (control) and cells transfected with the catalytically inactive mutated phosphatase mPAC1 (Cys^{257}/Ser) and human MKP1. The activity of p38 MAP kinase was measured with an immunecomplex protein kinase assay employing [γ-^{32}P]ATP and GST-ATF2 as substrates. The expression of PAC1 or MKP1 was found to inhibit p38 phosphorylation, demonstrating that p38 can be regulated by the dual specificity phosphatases PAC1 and MKP1.

Example 20. Subcellular Distribution of p38 MAP Kinase

Epitope-tagged p38 MAP kinase was expressed in COS cells. The cells were treated without or with 40 J/m^2 UV radiation and then incubated for 60 minutes at 37°C. The p38 MAP kinase was detected by indirect immunofluorescence using the M2 monoclonal antibody. The images were acquired by digital imaging microscopy and processed for image restoration.

Immunocytochemistry

Coverslips (22mm x 22mm No. 1; Gold Seal Cover Glass; Becton-Dickinson) were pre-treated by boiling in 0.1 N HCl for 10 minutes, rinsed in distilled water, autoclaved and coated with 0.01% poly-L-lysine (Sigma; St. Louis MO). The coverslips were placed at the bottom of 35 mm multiwell tissue culture plates (Becton Dickinson, UK). Transfected COS-1 cells were plated directly on the coverslips and allowed to adhere overnight in Dulbecco's modified Eagle's medium supplemented with 5% fetal calf serum (Gibco-BRL). Twenty-four hours post-transfection, the cells were rinsed once and incubated at 37°C for 30 minutes in 25 mM Hepes, pH 7.4, 137 mM NaCl, 6 mM KCl, 1 mM $MgCl_2$, 1 mM

$CaCl_2$, 10 mM glucose. The cells were rinsed once with phosphate-buffered saline and the coverslips removed from the tissue culture wells. Cells were fixed in fresh 4% paraformaldehyde in phosphate-buffered saline for 15 minutes at 22°C. The cells were permeabilized with 0.25% Triton® X-100 in phosphate-buffered saline for 5 minutes and washed three times in DWB solution (150 mM NaCl, 15 mM Na citrate, pH 7.0, 2% horse serum, 1% (w/v) bovine serum albumin, 0.05% Triton® X-100) for 5 minutes. The primary antibody (M2 anti-FLAG monoclonal antibody, Eastman-Kodak Co., New Haven, CT) was diluted 1:250 in DWB and applied to the cells in a humidified environment at 22°C for 1 hour. The cells were again washed three times as above and fluorescein isothiocyanate-conjugated goat anti-mouse Ig secondary antibody (Kirkegaard & Perry Laboratories Inc. Gaithersburg, MD) was applied at a 1:250 dilution for 1 hour at 22°C in a humidified environment. The cells were then washed three times in DWB and then mounted onto slides with Gel-Mount (Biomeda Corp. Foster City, CA) for immunofluorescence analysis. Control experiments were performed to assess the specificity of the observed immunofluorescence. No fluorescence was detected when the transfected cells were stained in the absence of the primary M2 monoclonal antibody, or mock-transfected cells.

Digital Imaging Microscopy and Image Restoration

Digital images of the fluorescence distribution in single cells were obtained using a Nikon 60x Planapo objective (numerical aperture = 1.4) on a Zeiss IM-35 microscope equipped for epifluorescence as previously described (Carrington et al. (1990) in: Non-invasive Techniques in Cell Biology, Fosbett & Grinstein, eds., Wiley-Liss, NY; pp. 53-72; Fay et al. (1989) J. Microsci. 153:133-149). Images of various focal planes were obtained with a computer controlled focus mechanism and a

thermoelectrically cooled charged-coupled device camera (model 220; Photometrics Ltd., Tucson, AZ). The exposure of the sample to the excitation source was determined by a computer-controlled shutter and wavelength selector system (MVI, Avon, MA). The charge-coupled device camera and microscope functions were controlled by a microcomputer, and the data acquired from the camera were transferred to a Silicon Graphics model 4D/GTX workstation (Mountainview, CA) for image processing. Images were corrected for non-uniformities in sensitivity and for the dark current of the charge coupled device detector. The calibration of the microscopy blurring was determined by measuring the instrument's point spread function as a series of optical sections at 0.125μm intervals of a 0.3 μm diameter fluorescently labeled latex bead (Molecular Probes Inc.). The image restoration algorithm used is based upon the theory of ill-posed problems and obtains quantitative dye density values within the cell that are substantially more accurate than those in an unprocessed image (Carrington et al. (1990) *supra*; Fay et al. (1989) *supra*). After image processing, individual optical sections of cells were inspected and analyzed using computer graphics software on a Silicon Graphics workstation. p38 MAP kinase was observed at the cell surface, in the cytoplasm, and in the nucleus. After irradiation, an increased localization of cytoplasmic p38 to the perinuclear region was detected.

Example 21. <u>Activation of the MKK Signal Transduction Pathway by Osmotic Shock</u>

CHO cells were co-transfected with the plasmid pCMV-Flag-Jnk1 and pRSV-Neo (Dérijard et al. (1994) *supra*). A stable cell line expressing epitope-tagged Jnk1 (Flag; Immunex Corp.) was isolated by selection with

Geneticin (Gibco-BRL). The cells were incubated with 0, 100, 150, 300, 600, or 1000 mM sorbitol for 1 hour at 37°C. The cells were collected in lysis buffer (20 mM Tris, pH 7.4, 1% TRITON® X-100, 2 mM EDTA, 137 mM NaCl, 25 mM β-glycerophosphate, 1 mM orthovanadate, 2 mM pyrophosphate, 10% glycerol, 1 mM phenylmethylsulfonyl fluoride, 10 μg/ml leupeptin) and a soluble extract was obtained by centrifugation at 100,000 g for 30 minutes at 4°C. The epitope-tagged JNK1 was isolated by immunoprecipitation with the monoclonal antibody M2 (Immunex Corp.). The immunoprecipitates were washed extensively with lysis buffer. Immunecomplex kinase assays were done in 25 μl of 25 mM Hepes, pH 7.4, 25 mM $MgCl_2$, 25 mM β-glycerophosphate, 2 mM dithiothreitol, 100 μM orthovanadate, and 50 μM ATP [γ-^{32}P] (10 Ci/mmole) with 2.5 μg of bacterially expressed c-Jun (residues 1-79) fused to glutathione-S-transferase (GST) as a substrate. The phosphorylation of c-Jun was examined after SDS-PAGE by autoradiography and PhosphorImager (Molecular Dynamics Inc.) analysis. JNK1 activation was observed at all concentrations of sorbitol exposure.

The time course of JNK1 protein kinase activation was measured in cells incubated in medium supplemented with 300 mM sorbitol as described above. Increased JNK1 activity was observed within 5 minutes of exposure to sorbitol, with maximum activity occurring after 15-30 minutes.

Mutation of JNK1 at the phosphorylation sites Thr^{183} and Tyr^{185} blocked the activation of JNK1 protein kinase activity by osmotic shock. CHO cells were transfected with vector, wild-type JNK1 (Thr^{183}, Tyr^{185}), and mutated JNK1 (Ala^{183}, Phe^{185}). The cells were incubated in medium supplemented without or with 300 mM sorbitol for 15 minutes before measurement of JNK1 protein kinase

activity as described above. JNK1 activation was seen in the wild-type but not mutated JNK1.

Example 22. <u>Molecular Cloning of MKK7</u>

RT-PCR was employed to identify a fragment of a novel mammalian MAP kinase kinase. The primers designed for the protocol, ATNGCNGTNAARCARATG (SEQ ID NO:23) and ATNCKYTCNGGNGCCATRTA (SEQ ID NO:24), were based on the sequence of the Drosophila MAP kinase kinase *hep* (Glise et al. (1995) Cell 83:451-461). Murine testis mRNA was used as the template. A single product (461 bp) was detected following RT-PCR amplification of murine testis mRNA. Sequence analysis identified this PCR product as a fragment of a novel mammalian MAP kinase kinase. Full-length murine cDNA clones were isolated by screening a murine testis library (Stratagene Inc.). The cDNA clones were examined by sequencing with an Applied Biosystems model 373A machine. A group of seven clones was identified by sequence analysis to contain a single long open reading frame that encoded a putative protein kinase (Fig. 9 and Fig. 10; SEQ ID NO:17 and SEQ ID NO:18). In-frame termination codons were detected in the 5′ and 3′ regions of these clones. This sequence includes protein kinase sub-domains I - XI and is related to the MAP kinase kinase group. The novel protein kinase was designated MKK7. The sites of activating phosphorylation of MAP kinase kinases located in sub-domain VIII are conserved in MKK7. Comparison of MKK7 with other members of the mammalian MAP kinase kinase group demonstrates that MKK7 is related to the JNK activator MKK4. One additional cDNA clone isolated from the λ phage library differed from the other seven clones. This clone contained the same 3′ untranslated region and coding region of MKK7, but had a different 5′ region that lacked an in-frame termination codon. This clone

represents an alternatively spliced form of MKK7 (MKK7b; Fig. 11; SEQ ID NO:19). The MKK7b cDNA clone does not have an initiation codon in the alternative 5′ region; this cDNA therefore encodes the same MKK7 protein kinase as the other clones that were isolated. However, if the MKK7b cDNA clone is not full-length it is possible that additional 5′ sequence may include an in-frame initiation codon. If true, MKK7b is predicted to fuse the sequence M-[?]-SPAPAPSQRAALQLPLANDGGSRSPSSESSPQHPTPPTRPRH- (SEQ ID NO:33) to the initiating methionine of MKK7 (Fig. 9). Although the Drosophila MAP kinase kinase *hep* shares substantial sequence similarity with MKK7, the sequence of the NH2-terminal extension of MKK7b is not conserved in the *hep* protein kinase. Three additional clones encoded MKK7 splice variants that differ in the 5′ and 3′ regions. These clones (MKK7c (Fig. 13), MKK7d (Fig. 14), and MKK7e (Fig. 15)) are full-length because of the presence of in-frame termination codons in the 5′ and 3′ regions.

A human cDNA library was screened with a full-length mouse MKK7 cDNA probe. A single clone was identified and squenced. A partial MKK7 sequence was identified (Fig. 12; SEQ ID NO:25 and SEQ ID NO:26) that is missing the 3′ end. The sequence is most homologous to mouse MKK7c.

The sequences of MKK7, MKK7b, hep, and human MKK7 cDNAs have been deposited in Genbank with accession numbers U93030, U93031, U93032, and AFOO319 respectively.

Example 23. <u>Expression of MKK7</u>

MKK7 expression was examined by Northern blot analysis of mRNA isolated from different tissues. The analysis was done with poly A+ mRNA (2 μg) isolated from different tissues and fractionated by denaturing agarose gel electrophoresis and transferred to a nylon membrane

(Clontech). The blot was probed with MKK4 and MKK7 cDNAs labeled by random priming with [α-^{32}P]dATP (Amersham International PLC).

MKK7 was found to be widely expressed in murine tissues. A single MKK7 transcript (approximately 4.0-kb) was detected in all of the tissues examined, except for testis where two MKK7 transcripts (4.0 kb and 1.5 kb) were detected. The highest levels of MKK7 expression were in testis. Significant expression of MKK7 was also observed in heart, brain, lung, liver, and kidney. This contrasts with MKK4 expression which was highest in brain although significant amounts of expression were observed in brain, liver, muscle, heart, and kidney. Although MKK4 and MKK7 are co-expressed, the relative abundance of each MAP kinase kinase is different in each of the tissues examined.

Example 24. Specific Activation of JNK by MKK7 *in vitro*

To examine the specificity of MKK7, *in vitro* protein kinase assays were performed. A bacterial MKK7 expression vector was prepared by sub-cloning an MKK7 cDNA (*Eco* RI and *Pvu* II fragment) into the *Eco* RI and *Sma* I sites of pGEX-5X1 (Pharmacia-LKB). The glutathione-S-transferase (GST) fusion protein was purified by affinity chromatography (Smith and Johnson (1988) Gene 67:31-40). The recombinant proteins GST-ATF2 (Gupta et al. (1995) Science 267:389-393), GST-cJun (Dérijard (1994) *supra*), GST-cMyc (Alvarez et al. (1991) J. Biol. Chem. 266:15277-15285), GST-ERK2 (Seth et al. (1992) J. Biol. Chem. 267:24796-24804), GST-p38, (Raingeaud et al. (1995) J. Biol. Chem. 270:7420-7426), and GST-JNK1 (Dérijard (1994) *supra*) have been described.

Protein kinase assays were performed in kinase buffer (25 mM 4-(2-hydroxyethyl)-1--piperazineethansulfonic acid (pH 7.4), 25 mM β-glycerophosphate, 25 mM $MgCl_2$, 2 mM dithiothreitol, 0.1 mM

orthovanadate). The assays were initiated by the addition of 1 μg of substrate proteins and 50 μM [γ-32P]ATP (10 Ci/mmol) in a final volume of 25 μl. The reactions were terminated after 30 minutes at 25°C by addition of Laemmli sample buffer. The phosphorylation of the substrate proteins was examined after SDS-polyacrylamide gel electrophoresis (PAGE) by autoradiography.

Recombinant MAP kinases were incubated with GST (control) or GST-MKK7 using the substrate ATP[γ-^{32}P]. Recombinant MKK7 purified from bacteria was not observed to autophosphorylate. Incubation of the recombinant MKK7 with MAP kinases demonstrated that MKK7 phosphorylated JNK1, but not p38 or ERK2. MKK7 was phosphorylated by p38 and JNK1. The significance of the retrophosphorylation of the MAP kinase kinase by the MAP kinase is unclear, but similar retrophosphorylation has been detected in kinase assays using MKK4 (Dérijard (1995) *supra*) and the Drosophila JNK activator *hep* (Sluss (1996) *supra*).

To test whether the phosphorylation of JNK1 by MKK7 caused increased protein kinase activity, experiments using ATF2 as the JNK substrate were performed. GST-MKK7 was incubated in a protein kinase assay with recombinant JNK1. JNK activity was measured by including the JNK substrate ATF2 in each assay. ATF2 was not phosphorylated by MKK7, but was weakly phosphorylated by JNK1. Incubation of MKK7 with JNK1 caused phosphorylation of JNK1 and a large increase in ATF2 phosphorylation. These data indicate that MKK7 phosphorylates and activates JNK1. To confirm this conclusion, the effect of replacement of the JNK dual phosphorylation motif Thr-Pro-Tyr with Ala-Pro-Phe was examined. MKK7 did not phosphorylate the mutated JNK1 (APF) protein. Furthermore, MKK7 did not increase ATF2

phosphorylation by the mutated JNK1 protein kinase. Thus, MKK7 is a JNK activator *in vitro*.

Example 25. <u>Specific Activation of JNK by MKK7 *in vivo*</u>

To examine the specificity of MKK7 *in vivo*, cotransfection assays were performed. CHO cells were maintained in Dulbecco's modified Eagle's medium supplemented with fetal calf serum (5%; Gibco-BRL). The cells were transfected with the lipofectamine reagent according to the manufacturer's recommendations (Gibco-BRL)(Dérijard (1994) *supra*). Cells were co-transfected with vectors encoding epitope-tagged JNK1 together with an empty expression vector (control) or an expression vector encoding MKK4 or MKK7. The epitope tag was derived from the hemagglutinin protein (HA) of the influenza virus. JNK1 was isolated by immunoprecipitation of cell lysates. The cells were solubilized with lysis buffer (20 mM Tris (pH 7.4), 1% TRITON X-100®, 10% glycerol, 137 mM NaCl, 2 mM EDTA, 25 mM β-glycerophosphate, 1 mM Na orthovanadate, 2 mM pyrophosphate, 1 mM PMSF, 10 μg/ml leupeptin) and centrifuged at 100,000 X g for 15 minutes at 4°C. The epitope-tagged protein kinases were immunoprecipitated by incubation for 3 hours at 4°C with an anti-HA monoclonal antibody bound to protein-G Sepharose (Pharmacia-LKB Biotechnology Inc.). The immunoprecipitates were washed three times with lysis buffer (Gupta et al. (1995) Science 267:389-393). Protein kinase activity was measured in the immunecomplex with [γ-^{32}P]ATP and c-Jun as substrates. The product of the phosphorylation reaction was visualized after SDS-PAGE by autoradiography. The ERK2 and p38 MAP kinases were not activated by co-expressed MKK7. Control experiments demonstrated that the ERK2 and p38 MAP kinases were activated by their respective cognate MAP kinase kinases, MKK1 and MKK6. In

contrast, MKK7 did activate JNK1. Interestingly, the activation of JNK1 by co-expressed MKK7 was greater than that caused by the previously described JNK activator MKK4. Together, these data establish that MKK7 can function as a specific activator of JNK in cultured cells.

Example 26. Activation of the JNK Signal Transduction Pathway by MKK7

The JNK signaling pathway is known to regulate AP-1 transcriptional activity (Whitmarsh (1996) *supra*). To test the hypothesis that the expression of MKK7 would cause increased AP-1 transcriptional activity, a co-transfection assay was employed using a luciferase reporter gene that contains three AP-1 sites cloned upstream of a minimal promoter element (Rincon and Flavell (1994) EMBO J. 13:4370-4381). Luciferase reporter gene expression was measured in co-transfection assays using the 0.5 μg of the reporter plasmid pTRE-luciferase (Rincon (1994) *supra*) and 0.25 μg of the β-galactosidase expression vector pCH110 (Pharmacia-LKB). Experiments using GAL4 fusion proteins were performed using 0.25 μg of pGAL4-ATF2 (residues 1-109), 0.5 μg of the reporter plasmid pG5E1bLuc, and 0.25 μg of pCH110 (Gupta et al. (1995) *supra*). The effect of protein kinases was examined by co-transfection with 0.3 μg of an empty expression vector or a protein kinase expression vector. The ERK2, p38, JNK1, MKK1, MKK3, MKK4, and MKK6 expression vectors have been described. The cells were harvested 36 hours post-transfection. The β-galactosidase and luciferase activity in the cell lysates was measured as described (Gupta (1995) *supra*). Expression of MKK4, MKK7, or JNK1 did not cause marked changes in AP-1 reporter gene expression (Fig. 16A). In contrast, co-expression of MKK7 with JNK1 caused

increased AP-1-dependent reporter gene expression. Consistent with the observation that MKK4 causes weaker activation of JNK than MKK7, co-expression of MKK4 with JNK caused a smaller increase in AP-1 reporter gene expression (Fig. 16A). Together, these data demonstrate that MKK7 can function as an activator of the JNK signal transduction pathway.

To further examine the effect of MKK7 on transcriptional activity, the effect of MKK7 on the transcription factor ATF2 was investigated. Previous studies have demonstrated that ATF2 is a target of the JNK signal transduction pathway (van Dam et al. (1995) *supra*; Gupta et al. (1995) *supra*; Livingstone et al (1995) *supra*). JNK phosphorylates two sites (Thr-69 and Thr-71) in the NH_2-terminal activation domain of ATF2 and increases transcriptional activity. A GAL4 fusion protein strategy was employed to monitor the transcriptional activity of the activation domain of ATF2 (Gupta (1995) *supra*). Measurement of reporter gene expression demonstrated that the coexpression of MKK4 with JNK1 caused increased transcriptional activity (Fig. 16B). A similar level of reporter gene expression was caused by expression of MKK7 and a larger increase was detected when MKK7 was co-expressed with JNK1. The more potent effect of MKK7, compared with MKK4, on transcriptional activity is consistent with the relative effects of MKK7 and MKK4 on JNK activation. To confirm that the increased reporter gene expression was mediated by ATF2 phosphorylation, the effect of replacement of the sites of ATF2 phosphorylation (Thr-69 and Thr-71) with Ala was examined. The mutated ATF2 protein was not regulated by MKK4, MKK7, or JNK1 (Fig. 16B). Together, these data demonstrate that MKK7 can regulate a physiological target of the JNK signaling pathway.

Use

The MKK polypeptides and polynucleotides of the invention are useful for identifying reagents that modulate the MKK signal transduction pathways. Reagents that modulate an MKK signal transduction pathway can be identified by their effect on MKK synthesis, MKK phosphorylation, or MKK activity. For example, the effect of a reagent on MKK activity can be measured by the *in vitro* kinase assays described above. MKK is incubated without (control) and with a test reagent under conditions sufficient to allow the components to react, then the effect of the test reagent on kinase activity is subsequently measured. Reagents that inhibit an MKK signal transduction pathway can be used in the treatment of MKK-mediated disorders. Reagents that stimulate an MKK signal transduction pathway can be used in a number of ways, including induction of programmed cell death (apoptosis) in tissues. For example, the elimination of UV damaged cells can be used to prevent cancer.

Generally, for identification of a reagent that inhibits the MKK signal transduction pathway, a kinase assay (see, for example, Example 3) is used. A range of reagent concentrations (e.g., 1.0 nM to 100 mM) are added to a test system that includes an MKK substrate and a radioactive marker such as [γ-^{32}P]ATP. Appropriate substrate molecules include p38, JNK1, JNK2, or ATF2. The incorporation of labelled phosphorus (e.g., [^{32}]P or [^{33}]P) into the substrate is determined, and the results obtained with the test reagent compared to control values. Of particular interest are reagents that result in inhibition of [^{32}]P incorporation of about 80% or more. Phosphorylation may also be examined using a reagent that is phosphorylation-dependent, for example, an antibody. Phosphorylation-dependent antibodies may be made using MKK7 phosphorylated on the activating sites, Ser^{198} and

Thr^{202}. This may be accomplished by immunizing animals with a synthetic peptide (for example, approximately 15 amino acids in length) corresponding to the MKK7 sequence with phosphorylated Ser^{198} and Thr^{202}. Methods of producing such antibodies are known in the art. Such antibodies are useful for the detection of activated MKK7 in tissues and cell extracts (e.g. on Western blots) and may be used in a kit.

Assays that test the effect of a reagent on MKK synthesis can also be used to identify compounds that inhibit MKK signal transduction pathways. The effect of the test reagent on MKK expression is measured by, for example, Western blot analysis with an antibody specific for an MKK. Antibody binding is visualized by autoradiography or chemiluminescence, and is quantitated. The effect of the test reagent on MKK mRNA expression can be examined, for example, by Northern blot analysis using a polynucleotide probe or by polymerase chain reaction.

Reagents found to inhibit MKK signal transduction pathways can be used as therapeutic agents for the treatment of MKK-mediated disorders. Such reagents are also useful in drug design for elucidation of the specific molecular features needed to inhibit MKK signal transduction pathways.

In addition, the invention provides a method for the treatment of MKK-mediated stress-related and inflammatory disorders. The method includes administration of an effective amount of a therapeutic reagent that inhibits MKK function. Suitable reagents inhibit either MKK activity or expression. The concentration of the reagent to be administered is determined based on a number of factors, including the appropriate dosage, the route of administration, and the specific condition being treated. The appropriate dose of a reagent is determined by methods known to those

skilled in the art including routine experimentation to optimize the dosage as necessary for the individual patient and specific MKK-mediated disorder being treated. Specific therapeutically effective amounts appropriate for administration are readily determined by one of ordinary skill in the art (see, for example, Remington's Pharmaceutical Sciences. 18th ed., Gennaro, ed., Mack Publishing Company, Easton, PA, 1990). Dosages may range from about 0.1-10 mg/kilo/day.

The invention provides methods for both acute and prophylactic treatment of stress-related and inflammatory disorders. For example, it is envisioned that ischemic heart disease will be treated during episodes of ischemia and oxidative stress following reperfusion. In addition, a patient at risk for ischemia can be treated prior to ischemic episodes.

In another example, a therapeutic agent that inhibits MKK function or activity is administered to control inflammatory responses by inhibiting the secretion of inflammatory cytokines, including TNF and IL-1.

Stress-related proliferative disorders can also be treated by the method of the invention by administering a therapeutic reagent that inhibits MKK function or activity. Such therapeutic reagents can be used alone or in combination with other therapeutic reagents, for example, with chemotherapeutic agents in the treatment of malignancies. Indeed, the control of stress-activated MKK by the therapeutic reagents provided by this invention can modulate symptoms caused by other therapeutic strategies that induce stress.

The therapeutic reagents employed are compounds which inhibit MKK function or activity, including polynucleotides, polypeptides, and other molecules such as antisense oligonucleotides and ribozymes, which can be

made according to the invention and techniques known to the art. Polyclonal or monoclonal antibodies (including fragments or derivatives thereof) that bind epitopes of MKK also can be employed as therapeutic reagents. Dominant-negative forms of MKK which effectively displace or compete with MKK for substrate binding and/or phosphorylation can be used to decrease protein kinase activity. Dominant-negative forms can be created by mutations within the catalytic domain of the protein kinases, using methods known in the art, and as described above (Example 13). The catalytic residues are conserved in all the MKK isoforms. For example, mutation of Lys^{76} inhibits MKK7 activity. Similarly, mutation of the conserved sites of activating phosphorylation (Ser^{198}, Thr^{202}) inhibits MKK7 activity. These kinase-inactive forms of MKK7 act as dominant-negative inhibitors.

In some cases, augmentation of MKK activity is desirable, e.g., induction of apoptosis. The methods of the invention can be used to identify reagents capable of increasing MKK function or activity. Alternatively, increased activity is achieved by over-expression of MKK. When an MKK-mediated disorder is associated with under-expression of MKK, or expression of a mutant MKK polypeptide, a sense polynucleotide sequence (the DNA coding strand) or MKK polypeptide can be introduced into the cell to enhance normal MKK activity. If necessary, these treatments are targeted to specific cells by their mode of administration (e.g., by use of cell-type specific viral vectors), or by placing MKK7 nucleic acids in recombinant constructs with cell-type specific or inducible promotors by methods known in the art. For example, MKK7 nucleic acid-containing vectors can be constructed by recombinant DNA technology methods standard in the art. Vectors can be plasmid, viral, or others known in the art, used for replication and

expression in mammalian cells. Expression of the sequence encoding the MKK7 nucleic acid can be by any promoter known in the art to act in mammalian, preferably human cells. Such promoters can be inducible or constitutive. Such promoters include, but are not limited to: the SV40 early promoter region (Bernoist et al., *Nature* 290:304, 1981); the promoter contained in the 3′ long terminal repeat of Rous sarcoma virus (Yamamoto et al., *Cell* 22:787-797, 1988); the herpes thymidine kinase promoter (Wagner et al., *Proc. Natl. Acad. Sci. USA* 78:1441, 1981); or the regulatory sequences of the metallothionein gene (Brinster et al., *Nature* 296:39, 1988).

The antibodies of the invention can be administered parenterally by injection or by gradual infusion over time. The monoclonal antibodies of the invention can be administered intravenously, intraperitoneally, intramuscularly, subcutaneously, intracavity, or transdermally.

Preparations for parenteral administration of a polypeptide or an antibody of the invention include sterile aqueous or non-aqueous solutions, suspensions, and emulsions. Examples of non-aqueous solvents are propylene glycol, polyethylene glycol, vegetable oils such as olive oil, and injectable organic esters such as ethyl oleate. Aqueous carriers include water, alcoholic/aqueous solutions, emulsions or suspensions, including saline and buffered media. Parenteral vehicles include sodium chloride solution, Ringer's dextrose, dextrose and sodium chloride, lactated Ringer's, or fixed oils. Intravenous vehicles include fluid and nutrient replenishers, electrolyte replenishers (such as those based on Ringer's dextrose) and the like. Preservatives and other additives can also be present, such as, for

example, antimicrobials, antioxidants, chelating agents, and inert gases, and the like.

Polynucleotide sequences, including antisense sequences, can be therapeutically administered by various techniques known to those skilled in the art. Such therapy would achieve its therapeutic effect by introduction of the MKK polynucleotide into cells of mammals having a MKK-mediated disorder. Delivery of MKK polynucleotides can be achieved using free polynucleotide or a recombinant expression vector such as a chimeric virus or a colloidal dispersion system. Especially preferred for therapeutic delivery of nucleotide sequences is the use of targeted liposomes.

Targeting of the therapeutic reagent to specific tissues is desirable to increase the efficiency of delivery. The targeting can be achieved by passive mechanisms via the route of administration. Active targeting to specific tissues can also be employed. The use of liposomes, colloidal suspensions, and viral vectors allows targeting to specific tissues by changing the composition of the formulation containing the therapeutic reagent, for example, by including molecules that act as receptors for components of the target tissues. Examples include sugars, glycoplipids, polynucleotides, or proteins. These molecules can be included with the therapeutic reagent. Alternatively, these molecules can be included by indirect methods, for example, by inclusion of a polynucleotide that encodes the molecule, or by use of packaging systems that provide targeting molecules. Those skilled in the art will know, or will ascertain with the use of the teaching provided herein, which molecules and procedures will be useful for delivery of the therapeutic reagent to specific tissues.

Transgenic animals

MKK polypeptides can also be expressed in transgenic animals. These animals represent a model system for the study of disorders that are caused by or exacerbated by overexpression or underexpression of MKK, and for the development of therapeutic agents that modulate the expression or activity of MKK. For example, dominant-negative and constitutively activated alleles could be expressed in mice to establish physiological function.

Transgenic animals can be farm animals (pigs, goats, sheep, cows, horses, rabbits, and the like) rodents (such as rats, guinea pigs, and mice), non-human primates (for example, baboons, monkeys, and chimpanzees), and domestic animals (for example, dogs and cats). Transgenic mice are especially preferred.

Any technique known in the art can be used to introduce a MKK transgene into animals to produce the founder lines of transgenic animals. Such techniques include, but are not limited to, pronuclear microinjection (U.S. Pat. No. 4,873,191); retrovirus mediated gene transfer into germ lines (Van der Putten et al., *Proc. Natl. Acad. Sci., USA* 82:6148, 1985); gene targeting into embryonic stem cells (Thompson et al., *Cell* 56:313, 1989); and electroporation of embryos (Lo, *Mol. Cell. Biol.* 3:1803, 1983). Especially useful are the methods described in Yang et al. (*Proc. Natl Acac. Sci. USA* 94:3004-3009, 1997)

The present invention provides for transgenic animals that carry the MKK transgene in all their cells, as well as animals that carry the transgene in some, but not all of their cells. That is, the invention provides for mosaic animals. The transgene can be integrated as a single transgene or in concatamers, e.g., head-to-head tandems or head-to-tail tandems. The transgene can also

be selectively introduced into and activated in a particular cell type (Lasko et al., *Proc. Natl. Acad. Sci. USA* 89:6232, 1992). The regulatory sequences required for such a cell-type specific activation will depend upon the particular cell type of interest, and will be apparent to those of skill in the art.

When it is desired that the MKK transgene be integrated into the chromosomal site of the endogenous MKK gene, gene targeting is preferred. Briefly, when such a technique is to be used, vectors containing some nucleotide sequences homologous to an endogenous MKK gene are designed for the purpose of integrating, via homologous recombination with chromosomal sequences, into and disrupting the function of the nucleotide sequence of the endogenous gene. The transgene also can be selectively introduced into a particular cell type, thus inactivating the endogenous MKK gene in only that cell type (Gu et al., *Science* 265:103, 1984). The regulatory sequences required for such a cell-type specific inactivation will depend upon the particular cell type of interest, and will be apparent to those of skill in the art. These techniques are useful for preparing "knock outs" having no functional MKK gene.

Once transgenic animals have been generated, the expression of the recombinant MKK gene can be assayed utilizing standard techniques. Initial screening may be accomplished by Southern blot analysis or PCR techniques to determine whether integration of the transgene has taken place. The level of mRNA expression of the transgene in the tissues of the transgenic animals may also be assessed using techniques which include, but are not limited to, Northern blot analysis of tissue samples obtained from the animal, *in situ* hybridization analysis, and RT-PCR. Samples of MKK gene-expressing tissue can

also be evaluated immunocytochemically using antibodies specific for the MKK transgene product.

For a review of techniques that can be used to generate and assess transgenic animals, skilled artisans can consult Gordon (*Intl. Rev. Cytol.* 115:171-229, 1989), and may obtain additional guidance from, for example: Hogan et al. Manipulating the Mouse Embryo, Cold Spring Harbor Press, Cold Spring Harbor, NY, 1986);, Krimpenfort et al. (*Bio/Technology* 9:86, 1991), Palmiter et al. (*Cell* 41:343, 1985), Kraemer et al. (Genetic Manipulation of the Early Mammalian Embryo, Cold Spring Harbor Press, Cold Spring Harbor, NY, 1985), Hammer et al.(*Nature* 315:680, 1985), Purcel et al. (*Science*, 244:1281, 1986), Wagner et al. (U.S. Patent No. 5,175,385), and Krimpenfort et al. (U.S. Patent No. 5,175,384) (the latter two publications are hereby incorporated by reference).

Other Embodiments

It is to be understood that while the invention has been described in conjunction with the detailed description thereof, that the foregoing description is intended to illustrate and not limit the scope of the invention, which is defined by the scope of the appended claims. Other aspects, advantages, and modifications are within the scope of the following claims.

CLAIMS

1. A substantially pure mammalian mitogen-activated protein kinase kinase (MKK7) polypeptide having serine, threonine, and tyrosine kinase activity, and phosphorylating mitogen-activated protein (MAP) kinase JNK, but not p38.

2. A polypeptide of claim 1 comprising the amino acid sequence of SEQ ID NO:18, SEQ ID NO:20, SEQ ID NO:26, SEQ ID NO:28, SEQ ID NO:30, or SEQ ID NO:32.

3. An isolated polynucleotide sequence encoding a polypeptide of claim 1.

4. An isolated polynucleotide sequence of claim 3 comprising the sequence of SEQ ID NO:17, SEQ ID NO:19, SEQ ID NO:25, SEQ ID NO:27, SEQ ID NO:29, or SEQ ID NO:31, or degenerate variants thereof, or a polynucleotide sequence fully complementary to the sequence of SEQ ID NO:17, SEQ ID NO:19, SEQ ID NO:25, SEQ ID NO:27, SEQ ID NO:29, or SEQ ID NO:31, or degenerate variants thereof.

5. An isolated polynucleotide sequence of claim 3 comprising a polynucleotide sequence that hybridizes under stringent hybridization conditions to the sequence of SEQ ID NO:17, SEQ ID NO:19, SEQ ID NO:25, SEQ ID NO:27, SEQ ID NO:29, SEQ ID NO:31, or a complement thereof.

6. A recombinant expression vector containing a polynucleotide sequence of claim 3.

7. A recombinant host cell comprising a polynucleotide sequence of claim 3.

8. A purified antibody that binds specifically to a polypeptide of claim 1.

9. A purified antibody that binds specifically to a polypeptide of claim 2.

10. A method of measuring the activity of a mitogen-activated protein kinase kinase (MKK7) in a biological test sample, said method comprising:

a) incubating said test sample with an MKK substrate for the MKK polypeptide of claim 1 and labeled phosphate under conditions sufficient to allow phosphorylation of said substrate; and

b) determining the rate of incorporation of labeled phosphate into said substrate, wherein said rate of incorporation is a measure of MKK7 activity.

11. A method of claim 10, wherein said MKK substrate is selected from the group consisting of JNK MAP kinases, activating transcription factor-2 (ATF2), ATFa, cAMP response element binding protein (CRE-BPa), and c-Jun.

12. A method of claim 10, wherein said biological test sample is fluid, cells, or tissue obtained from a mammal.

13. A method for measuring the synthesis of MKK7 in a biological test sample, the method comprising the steps of:

a) obtaining a biological sample;

b) contacting said biological sample with an antibody that specifically binds an MKK7 polypeptide of claim 1; and

c) detecting said antibody bound to MKK7 polypeptide, wherein the level of MKK7 synthesis is determined by the amount of bound antibody.

14. A method for measuring the level of expression of MKK7 in a test sample, the method comprising the steps of:

a) isolating total or polyadenylated RNA from the test sample;

b) incubating the RNA with a polynucleotide probe specific for an MKK7 polynucleotide of claim 3; and

c) determining the amount of said probe hybridized to the RNA, wherein the level of expression of MKK7 is directly related to the amount of MKK7 probe hybridized to the RNA.

15. A method for identifying a reagent that modulates MKK7 activity, said method comprising:

a) obtaining a test sample containing MKK7;

b) incubating said test sample with an MKK substrate for the MKK polypeptide of claim 1, a range of reagent concentrations, and labeled phosphate under conditions sufficient to allow phosphorylation of said subtrate when said reagent is not present;

c) detecting phosphorylation of said substrate; and

d) comparing the effect of said reagent on MKK7 activity relative to a control, wherein any variation compared to control indicates a reagent able to modulate MKK7 substrate phosphorylation.

16. A method of claim 15, wherein said MKK7 substrate is one or more of JNK, ATF2, ATFa, CRE-BPa, and c-Jun.

17. A method of claim 15 wherein said modulation is inhibition of MKK7 activity.

18. A method for identifying a reagent that modulates MKK7 synthesis, said method comprising:

a) providing a sample capable of MKK7 synthesis;

b) incubating said sample with a range of reagent concentrations under conditions that allow synthesis of MKK7 when said reagent is not present;

c) detecting an MKK7 polypeptide of claim 1; and

d) comparing the effect of said reagent on MKK7 synthesis relative to a control, wherein any variation compared to control indicates a reagent able to modulate MKK7.

19. A method of claim 18 wherein said modulation is inhibition of MKK7 synthesis.

20. A method for identifying a reagent that modulates MKK7 expression, said method comprising:

a) providing a sample capable of expressing MKK7;

b) incubating said sample with a range of concentrations of said reagent under conditions where MKK7 is expressed in the absence of said reagent;

c) isolating total or polyadenylated RNA from the sample;

d) incubating the RNA with a polynucleotide probe specific for a MKK7 nucleic acid of claim 3; and

e) comparing the effect of said reagent on MKK7 RNA expression relative to a control, wherein any variation compared to control indicates a reagent able to modulate MKK7 expression.

21. A method of treating an MKK7-mediated disorder in a patient, the method comprising administering to the patient a therapeutically effective amount of a reagent that modulates MKK7 activity.

22. The method of claim 21, wherein said MKK7-mediated disorder is selected from the group consisting of ischemic heart disease, kidney failure, oxidative liver damage, respiratory distress syndrome, heat and

radiation burns, septic shock, rheumatoid arthritis, autoimmune disorders, and inflammatory diseases.

23. A method of treating an MKK7-associated disorder in a patient, comprising administering to the patient a therapeutically effective amount of an MKK7 polypeptide.

24. The method of claim 23, wherein said MKK7-associated disorder is ischemic heart disease, kidney failure, oxidative liver damage, respiratory distress syndrome, heat and radiation burns, septic shock, rheumatoid arthritis, autoimmune disorders, or inflammatory diseases.

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                                                                            71
MKK3       MSKPP---------APNPTPPRN----------LDSRTFITIG------DRNFEVEADD
MKK4       MQGKRKALKLNFAN..FKSTARFTLN....GVQ.PHIERLRTHSIE.SGKLK.SP-----EQHWDFT.E.
MEK1       MPKKKP--TPIQLN.A-PDGSAVNGTSSAETNLEALQKKLEELE..EQQRKRLEAFLTQKQKVG.LKD..
MEK2       MLARRKPVLPALTIN.TIAEGPSPTSEGASEANLVDLQKKLEELE..EQQKKRLEAFLTQKAKVG.LKD..
PBS2       <GTTPRTGNSNNS-NSGSSGGGGLFANFSKYVDIKSGSLNFAGKLSL.SKG.DFSN-----GSSSRITL.E
Consensus

           72      I                    II              III          IV    142
MKK3       LVTISELGRGAYGVVEKVRHAQSGTIMAVKRIRATVNSQEQKRLLMDLDINMRTVDCFYTVTFYGALFREG
MKK4       .KDLG.I......S.N.MV.KP..Q........S..DEK...Q......VV..SS..P.I.Q.........
MEK1       FEK.....A.NG...F.VS.KP..LV..R.L.HLEIKPAIRNQIIRE.QV-LHECNSP.I.G....FYSD.
MEK2       FER.....A.NG...T.VQ.RP..L...R.L.HLEIKPAIRNQIIRE.QV-LHECNSP.I.G....FYSD.
PBS2       .EFLD...H.N..N.S.VL.KPTNV...T.EV.LELDEAKFRQI..E.EV-LHKCNSP.I.D....F.I..
Consensus       E G G  G V K  H     MA K                 L          Y V FYGA    G

           143   V                                               VI        213
MKK3       DVWICMELMD-TSLDKFYR---KVLDKNMTIPEDILGEIAVSIVRALEHLHSKLSVIHRDVKPSNVL-INK
MKK4       .C.......S-..F....KYVYS...D--V...E...K.TLAT.K..N..KEN.KI....I....I.-LDR
MEK1       EIS....H..GG...Q-------..K.AGR...Q...KVSIAVIKG.TY.RE.HKIM........I.-V.S
MEK2       EIS....H..GG...Q-------..KEAKR...E...KVSIAVL.G.AY.RE.HQIM........I.-V.S
PBS2       A.YM...Y..GG....IYDESSEIGG----.D.PQ.AF..NAVIHG.KE.KEQHNI.......T.I.CSAN
Consensus     CME M   S D                 I E  L          L  L       HRD KP N L

           214     VII        *   *       VIII                 IX              284
MKK3       EGHVKMCDFGISGYLVDSVAKTMDAGCKPYMAPERINP-ELNQKGYNVKSDVWSLGITMIEMAILRFPY--
MKK4       S.NI.L.......Q....I...R....R........D.-SASRQ..D.R.........LY.L.TG....--
MEK1       R.EI.L....V..Q.I..M.NSF-V.TRS..S...LQGTH-----.S.Q..I..M.LSLV...VG.Y.IPP
MEK2       R.EI.L....V..Q.I..M.NSF-V.TRS......LQGTH-----.S.Q..I..M.LSLV.L.VG.Y.IPP
PBS2       Q.T..L....V..N..A.L....NI..QS.......KSLNPDRAT.T.Q..I....LSIL...LG.Y..PP
Consensus   G  K CDFG SG L  S A     G    YM PER              Y V SD WS G    E A  R P

           285                                                  X              355
MKK3       ESWG-----------------------------------------TPFQQLKQVVEEPSPQLPAD---R
MKK4       PK.N-----------------------------------------SV.D..T...KGDP...SNSEERE
MEK1       PDAKELELMFGCQV----EGDAAETPPRPRTPGRPLSSYGMDSRPPMAI.EL.DYI.N..P.K..SGV---
MEK2       PDAKELEAIFGRPVVDGEEGEPHSISPRPRPPGRPVSGHGMDSRPAMAI.EL.DYI.N..P.K..NGV---
PBS2       .TYD-----------------------------------------NI.S..SAI.DG.P.R..S.---K
Consensus                                                    F  L   V    P L

           356                  XI                                          426
MKK3       FSPEFVDFTAQCLRKNPAERMSYLELMEHPFFTLHKTKKTDIAAFVK-------KILGEDS           (SEQ ID NO: 2)
MKK4       ...S.IN.VNL..T.DESK.PK.K..LK...ILMYEERAVEV.CY.C-------...DQMPATPSSPMYVD (SEQ ID NO: 6)
MEK1       ..L..Q..VNK..I......ADLKQ..V.A.IKRSDAEEV.F.GWLCSTIGLNQPSTPTHAAGV        (SEQ ID NO: 11)
MEK2       .T.D.QE.VNK..I......ADLKM.TN.T.IKRSEVEEV.F.GWLCKTLRLNQPGTPTRTA          (SEQ ID NO: 12)
PBS2       ..SDAQD.VSL..Q.I.ER.PT.AA.T..PWLVKYRNQDVHMSEYITERLERRN...R.RGENGLSKNVP> (SEQ ID NO: 13)
Consensus  F       F  CL K    R     L  H                                           (SEQ ID NO: 34)
```

FIG. 1

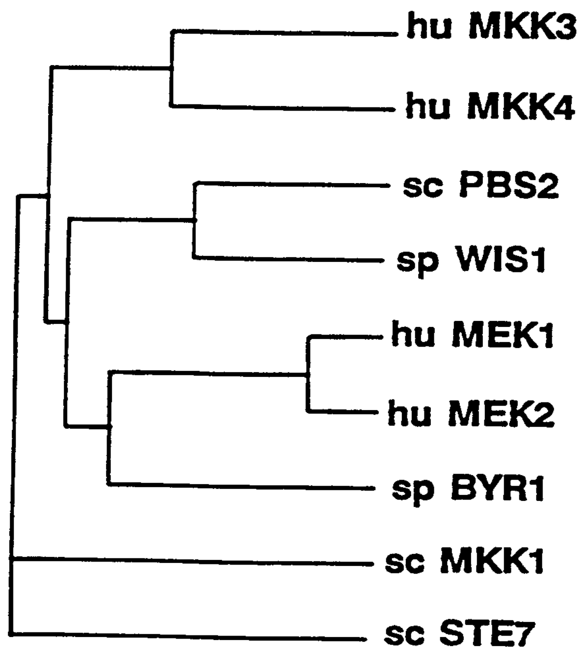
hu MKK3
hu MKK4
sc PBS2
sp WIS1
hu MEK1
hu MEK2
sp BYR1
sc MKK1
sc STE7

FIG. 2A

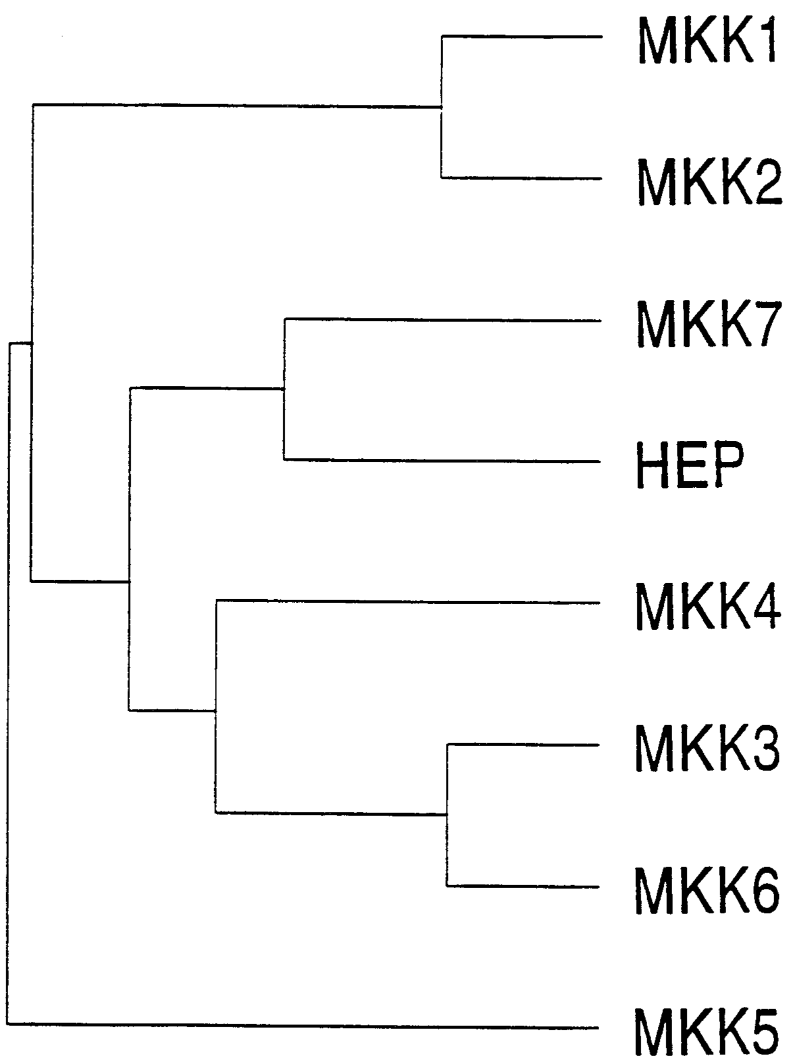

FIG. 2B

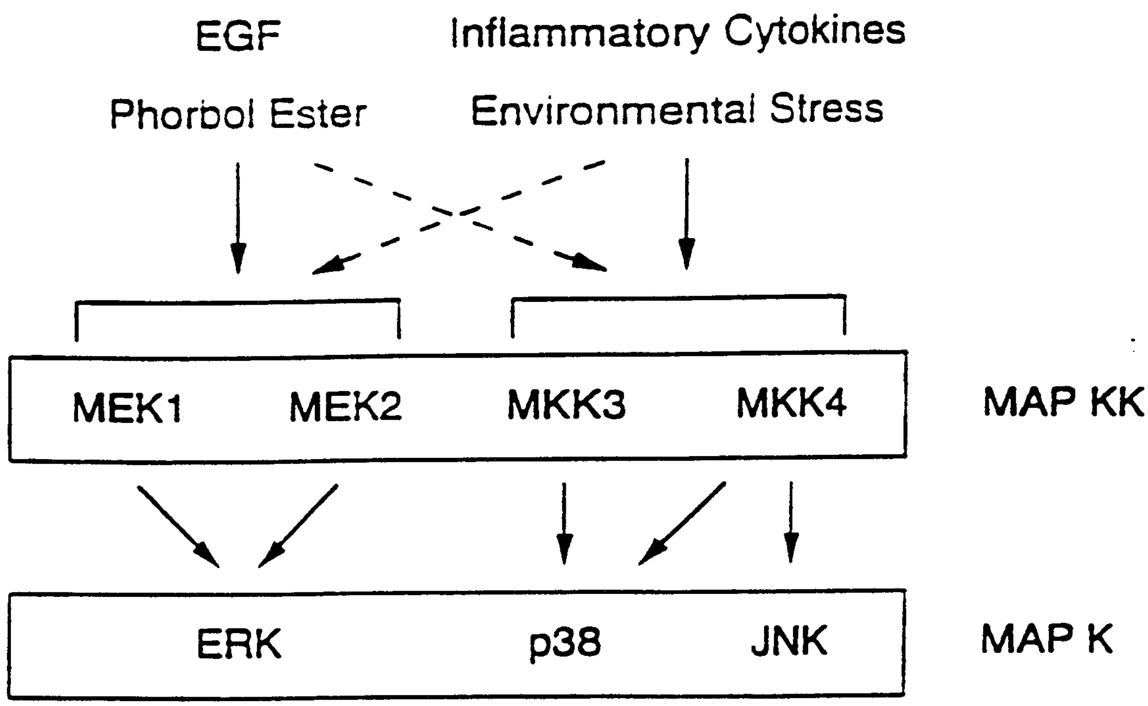
EGF
Phorbol Ester
Inflammatory Cytokines
Environmental Stress
MEK1
MEK2
MKK3
MKK4
MAP KK
ERK
p38
JNK
MAP K

FIG. 3

```
         5        10        15        20        25        30        35        40        45        50        55        60
TGGCTGGCAA TGGCCTTGCT GACCTCGAGC CGGGCCCACG TGGGGACCTT TGGAGCACAG
ACCGACCGTT ACCGGAACGA CTGGAGCTCG GCCCGGGTGC ACCCCTGGAA ACCTCGTGTC

        65        70        75        80        85        90        95       100       105       110       115       120
CCTACGATCC TGGTGCAAGG CCGGTGGATG CAGAGGCCAG TCCATATACC ACCCAGGCCT
GGATGCTAGG ACCACGTTCC GGCCACCTAC GTCTCCGGTC AGGTATATGG TGGGTCCGGA

       125       130       135       140       145       150       155       160       165       170       175       180
GCGAGGAGCG TGGTCCCCAC CCATCCAGCC CATATGTGCA AGTGCCCTTG ACAGAGAGGC
CGCTCCTCGC ACCAGGGGTG GGTAGGTCGG GTATACACGT TCACGGGAAC TGTCTCTCCG

       185       190       195       200       205       210       215       220       225       230       235       240
TGGTCATATC CATGGTGACC ATTTATGGGC CACAACAGGT CCCCATCTGC GCAGTGAACC
ACCAGTATAG GTACCACTGG TAAATACCCG GTGTTGTCCA GGGGTAGACG CGTCACTTGG

       245       250       255       260       265       270       275       280       285       290       295       300
CTGTGCTGAG CACCTTGCAG ACGTGATCTT GCTTCGTCCT GCAGCACTGT GCGGGGCAGG
GACACGACTC GTGGAACGTC TGCACTAGAA CGAAGCAGGA CGTCGTGACA CGCCCCGTCC

       305       310       315       320       325       330       335       340       345       350       355
AAAATCCAAG AGGAAGAAGG ATCTACGGAT ATCCTGC ATG TCC AAG CCA CCC GCA
TTTTAGGTTC TCCTTCTTCC TAGATGCCTA TAGGACG TAC AGG TTC GGT GGG CGT
                                         Met Ser Lys Pro Pro Ala>

       360       365       370       375       380       385       390       395       400
CCC AAC CCC ACA CCC CCC CGG AAC CTG GAC TCC CGG ACC TTC ATC ACC
GGG TTG GGG TGT GGG GGG GCC TTG GAC CTG AGG GCC TGG AAG TAG TGG
Pro Asn Pro Thr Pro Pro Arg Asn Leu Asp Ser Arg Thr Phe Ile Thr>

405       410       415       420       425       430       435       440       445       450
ATT GGA GAC AGA AAC TTT GAG GTG GAG GCT GAT GAC TTG GTG ACC ATC
TAA CCT CTG TCT TTG AAA CTC CAC CTC CGA CTA CTG AAC CAC TGG TAG
Ile Gly Asp Arg Asn Phe Glu Val Glu Ala Asp Asp Leu Val Thr Ile>

    455       460       465       470       475       480       485       490       495
TCA GAA CTG GGC CGT GGA GCC TAT GGG GTG GTA GAG AAG GTG CGG CAC
AGT CTT GAC CCG GCA CCT CGG ATA CCC CAC CAT CTC TTC CAC GCC GTG
Ser Glu Leu Gly Arg Gly Ala Tyr Gly Val Val Glu Lys Val Arg His>

500       505       510       515       520       525       530       535       540       545
GCC CAG AGC GGC ACC ATC ATG GCC GTG AAG CGG ATC CGG GCC ACC GTG
CGG GTC TCG CCG TGG TAG TAC CGG CAC TTC GCC TAG GCC CGG TGG CAC
Ala Gln Ser Gly Thr Ile Met Ala Val Lys Arg Ile Arg Ala Thr Val>

550       555       560       565       570       575       580       585       590       595
AAC TCA CAG GAG CAG AAG CGG CTG CTC ATG GAC CTG GAC ATC AAC ATG
TTG AGT GTC CTC GTC TTC GCC GAC GAG TAC CTG GAC CTG TAG TTG TAC
Asn Ser Gln Glu Gln Lys Arg Leu Leu Met Asp Leu Asp Ile Asn Met>
```

FIG. 4A

```
    600       605       610       615       620       625       630       635       640
CGC ACG GTC GAC TGT TTC TAC ACT GTC ACC TTC TAC GGG GCA CTA TTC
GCG TGC CAG CTG ACA AAG ATG TGA CAG TGG AAG ATG CCC CGT GAT AAG
Arg Thr Val Asp Cys Phe Tyr Thr Val Thr Phe Tyr Gly Ala Leu Phe>

645       650       655       660       665       670       675       680       685       690
AGA GAG GGA GAC GTG TGG ATC TGC ATG GAG CTC ATG GAC ACA TCC TTG
TCT CTC CCT CTG CAC ACC TAG ACG TAC CTC GAG TAC CTG TGT AGG AAC
Arg Glu Gly Asp Val Trp Ile Cys Met Glu Leu Met Asp Thr Ser Leu>

   695       700       705       710       715       720       725       730       735
GAC AAG TTC TAC CGG AAG GTG CTG GAT AAA AAC ATG ACA ATT CCA GAG
CTG TTC AAG ATG GCC TTC CAC GAC CTA TTT TTG TAC TGT TAA GGT CTC
Asp Lys Phe Tyr Arg Lys Val Leu Asp Lys Asn Met Thr Ile Pro Glu>

740       745       750       755       760       765       770       775       780       785
GAC ATC CTT GGG GAG ATT GCT GTG TCT ATC GTG CGG GCC CTG GAG CAT
CTG TAG GAA CCC CTC TAA CGA CAC AGA TAG CAC GCC CGG GAC CTC GTA
Asp Ile Leu Gly Glu Ile Ala Val Ser Ile Val Arg Ala Leu Glu His>

790       795       800       805       810       815       820       825       830       835
CTG CAC AGC AAG CTG TCG GTG ATC CAC AGA GAT GTG AAG CCC TCC AAT
GAC GTG TCG TTC GAC AGC CAC TAG GTG TCT CTA CAC TTC GGG AGG TTA
Leu His Ser Lys Leu Ser Val Ile His Arg Asp Val Lys Pro Ser Asn>

   840       845       850       855       860       865       870       875       880
GTC CTT ATC AAC AAG GAG GGC CAT GTG AAG ATG TGT GAC TTT GGC ATC
CAG GAA TAG TTG TTC CTC CCG GTA CAC TTC TAC ACA CTG AAA CCG TAG
Val Leu Ile Asn Lys Glu Gly His Val Lys Met Cys Asp Phe Gly Ile>

885       890       895       900       905       910       915       920       925       930
AGT GGC TAC TTG GTG GAC TCT GTG GCC AAG ACG ATG GAT GCC GGC TGC
TCA CCG ATG AAC CAC CTG AGA CAC CGG TTC TGC TAC CTA CGG CCG ACG
Ser Gly Tyr Leu Val Asp Ser Val Ala Lys Thr Met Asp Ala Gly Cys>

   935       940       945       950       955       960       965       970       975
AAG CCC TAC ATG GCC CCT GAG AGG ATC AAC CCA GAG CTG AAC CAG AAG
TTC GGG ATG TAC CGG GGA CTC TCC TAG TTG GGT CTC GAC TTG GTC TTC
Lys Pro Tyr Met Ala Pro Glu Arg Ile Asn Pro Glu Leu Asn Gln Lys>

980       985       990       995      1000      1005      1010      1015      1020      1025
GGC TAC AAT GTC AAG TCC GAC GTC TGG AGC CTG GGC ATC ACC ATG ATT
CCG ATG TTA CAG TTC AGG CTG CAG ACC TCG GAC CCG TAG TGG TAC TAA
Gly Tyr Asn Val Lys Ser Asp Val Trp Ser Leu Gly Ile Thr Met Ile>

1030      1035      1040      1045      1050      1055      1060      1065      1070      1075
GAG ATG GCC ATC CTG CGG TTC CCT TAC GAG TCC TGG GGG ACC CCG TTC
CTC TAC CGG TAG GAC GCC AAG GGA ATG CTC AGG ACC CCC TGG GGC AAG
Glu Met Ala Ile Leu Arg Phe Pro Tyr Glu Ser Trp Gly Thr Pro Phe>

   1080      1085      1090      1095      1100      1105      1110      1115      1120
```

FIG. 4B

```
CAG CAG CTG AAG CAG GTG GTG GAG GAG CCG TCC CCC CAG CTC CCA GCC
GTC GTC GAC TTC GTC CAC CAC CTC CTC GGC AGG GGG GTC GAG GGT CGG
Gln Gln Leu Lys Gln Val Val Glu Glu Pro Ser Pro Gln Leu Pro Ala>

1125  1130  1135  1140  1145  1150  1155  1160  1165  1170

GAC CGT TTC TCC CCC GAG TTT GTG GAC TTC ACT GCT CAG TGC CTG AGG
CTG GCA AAG AGG GGG CTC AAA CAC CTG AAG TGA CGA GTC ACG GAC TCC
Asp Arg Phe Ser Pro Glu Phe Val Asp Phe Thr Ala Gln Cys Leu Arg>

1175  1180  1185  1190  1195  1200  1205  1210  1215

AAG AAC CCC GCA GAG CGT ATG AGC TAC CTG GAG CTG ATG GAG CAC CCC
TTC TTG GGG CGT CTC GCA TAC TCG ATG GAC CTC GAC TAC CTC GTG GGG
Lys Asn Pro Ala Glu Arg Met Ser Tyr Leu Glu Leu Met Glu His Pro>

1220  1225  1230  1235  1240  1245  1250  1255  1260  1265

TTC TTC ACC TTG CAC AAA ACC AAG AAG ACG GAC ATT GCT GCC TTC GTG
AAG AAG TGG AAC GTG TTT TGG TTC TTC TGC CTG TAA CGA CGG AAG CAC
Phe Phe Thr Leu His Lys Thr Lys Lys Thr Asp Ile Ala Ala Phe Val>

1270  1275  1280  1285  1290  1295  1300  1305  1310  1315  1320

AAG AAG ATC CTG GGA GAA GAC TCA TAGGGGCTG GGCCTCGGAC CCCACTCCGG
TTC TTC TAG GAC CCT CTT CTG AGT ATCCCCGAC CCGGAGCCTG GGGTGAGGCC
Lys Lys Ile Leu Gly Glu Asp Ser> (SEQ ID NO:2)

1325 1330  1335 1340  1345 1350  1355 1360  1365 1370  1375 1380

CCCTCCAGAG CCCCACAGCC CCATCTGCGG GGGCAGTGCT CACCCACACC ATAAGCTACT
GGGAGGTCTC GGGGTGTCGG GGTAGACGCC CCCGTCACGA GTGGGTGTGG TATTCGATGA

1385 1390  1395 1400  1405 1410  1415 1420  1425 1430  1435 1440

GCCATCCTGG CCCAGGGCAT CTGGGAGGAA CCGAGGGGGC TGCTCCCACC TGGCTCTGTG
CGGTAGGACC GGGTCCCGTA GACCCTCCTT GGCTCCCCCG ACGAGGGTGG ACCGAGACAC

1445 1450  1455 1460  1465 1470  1475 1480  1485 1490  1495 1500

GCGAGCCATT TGTCCCAAGT GCCAAAGAAG CAGACCATTG GGGCTCCCAG CCAGGCCCTT
CGCTCGGTAA ACAGGGTTCA CGGTTTCTTC GTCTGGTAAC CCCGAGGGTC GGTCCGGGAA

1505 1510  1515 1520  1525 1530  1535 1540  1545 1550  1555 1560

GTCGGCCCCA CCAGTGCCTC TCCCTGCTGC TCCTAGGACC CGTCTCCAGC TGCTGAGATC
CAGCCGGGGT GGTCACGGAG AGGGACGACG AGGATCCTGG GCAGAGGTCG ACGACTCTAG

1565 1570  1575 1580  1585 1590  1595 1600  1605 1610  1615 1620

CTGGACTGAG GGGGCCTGGA TGCCCCCTGT GGATGCTGCT GCCCCTGCAC AGCAGGCTGC
GACCTGACTC CCCCGGACCT ACGGGGGACA CCTACGACGA CGGGGACGTG TCGTCCGACG

1625 1630  1635 1640  1645 1650  1655 1660  1665 1670  1675 1680

CAGTGCCTGG GTGGATGGGC CACCGCCTTG CCCAGCCTGG ATGCCATCCA AGTTGTATAT
GTCACGGACC CACCTACCCG GTGGCGGAAC GGGTCGGACC TACGGTAGGT TCAACATATA

1685 1690  1695 1700  1705 1710  1715 1720  1725 1730  1735 1740

TTTTTTAATC TCTCGACTGA ATGGACTTTG CACACTTTGG CCCAGGGTGG CCACACCTCT
```

FIG. 4C

```
AAAAAATTAG AGAGCTGACT TACCTGAAAC GTGTGAAACC GGGTCCCACC GGTGTGGAGA

 1745 1750  1755 1760  1765 1770  1775 1780  1785 1790  1795 1800
         *          *          *          *          *          *
ATCCCGGCTT TGGTGCGGGG TACACAAGAG GGGATGAGTT GTGTGAATAC CCCAAGACTC
TAGGGCCGAA ACCACGCCCC ATGTGTTCTC CCCTACTCAA CACACTTATG GGGTTCTGAG

 1805 1810  1815 1820  1825 1830  1835 1840  1845 1850  1855 1860
         *          *          *          *          *          *
CCATGAGGGA GATGCCATGA GCCGCCCAAG GCCTTCCCCT GGCACTGGCA AACAGGGCCT
GGTACTCCCT CTACGGTACT CGGCGGGTTC CGGAAGGGGA CCGTGACCGT TTGTCCCGGA

 1865 1870  1875 1880  1885 1890  1895 1900  1905 1910  1915 1920
         *          *          *          *          *          *
CTGCGGAGCA CACTGGCTCA CCCAGTCCTG CCCGCCACCG TTATCGGTGT CATTCACCTT
GACGCCTCGT GTGACCGAGT GGGTCAGGAC GGGCGGTGGC AATAGCCACA GTAAGTGGAA

 1925 1930  1935 1940  1945 1950  1955 1960  1965 1970  1975 1980
         *          *          *          *          *          *
TCGTGTTTTT TTTAATTTAT CCTCTGTTGA TTTTTTCTTT TGCTTTATGG GTTTGGCTTG
AGCACAAAAA AAATTAAATA GGAGACAACT AAAAAAGAAA ACGAAATACC CAAACCGAAC

 1985 1990  1995 2000  2005 2010  2015 2020  2025 2030
         *          *          *          *          *
TTTTTCTTGC ATGGTTTGGA GCTGATCGCT TCTCCCCCAC CCCCTAGGGG (SEQ ID NO: 1)
AAAAAGAACG TACCAAACCT CGACTAGCGA AGAGGGGGTG GGGGATCCCC
```

FIG. 4D

```
         5         10         15         20         25         30         35         40         45         50         55         60
TAGCTGCAGC ACAGCCTTCC CTAACGTTGC AACTGGGGGA AAAATCACTT TCCAGTCTGT
ATCGACGTCG TGTCGGAAGG GATTGCAACG TTGACCCCCT TTTTAGTGAA AGGTCAGACA

        65         70         75         80         85         90         95        100        105        110        115        120
TTTGCAAGGT GTGCATTTCC ATCTTGATTC CCTGAAAGTC CATCTGCTGC ATCGGTCAAG
AAACGTTCCA CACGTAAAGG TAGAACTAAG GGACTTTCAG GTAGACGACG TAGCCAGTTC

       125        130        135        140        145        150        155        160        165        170        175        180
AGAAACTCCA CTTGCATGAA GATTGCACGC CTGCAGCTTG CATCTTTGTT GCAAAACTAG
TCTTTGAGGT GAACGTACTT CTAACGTGCG GACGTCGAAC GTAGAAACAA CGTTTTGATC

       185        190        195        200        205        210        215        220        225        230        235        240
CTACAGAAGA GAAGCAAGGC AAAGTCTTTT GTGCTCCCCT CCCCCATCAA AGGAAAGGGG
GATGTCTTCT CTTCGTTCCG TTTCAGAAAA CACGAGGGGA GGGGGTAGTT TCCTTTCCCC

    245         250         255         260         265         270         275         280         285
AAA ATG TCT CAG TCG AAA GGC AAG AAG CGA AAC CCT GGC CTT AAA ATT
TTT TAC AGA GTC AGC TTT CCG TTC TTC GCT TTG GGA CCG GAA TTT TAA
    Met Ser Gln Ser Lys Gly Lys Lys Arg Asn Pro Gly Leu Lys Ile>

290         295         300         305         310         315         320         325         330         335
CCA AAA GAA GCA TTT GAA CAA CCT CAG ACC AGT TCC ACA CCA CCT AGA
GGT TTT CTT CGT AAA CTT GTT GGA GTC TGG TCA AGG TGT GGT GGA TCT
Pro Lys Glu Ala Phe Glu Gln Pro Gln Thr Ser Ser Thr Pro Pro Arg>

    340         345         350         355         360         365         370         375         380
GAT TTA GAC TCC AAG GCT TGC ATT TCT ATT GGA AAT CAG AAC TTT GAG
CTA AAT CTG AGG TTC CGA ACG TAA AGA TAA CCT TTA GTC TTG AAA CTC
Asp Leu Asp Ser Lys Ala Cys Ile Ser Ile Gly Asn Gln Asn Phe Glu>

385         390         395         400         405         410         415         420         425         430
GTG AAG GCA GAT GAC CTG GAG CCT ATA ATG GAA CTG GGA CGA GGT GCG
CAC TTC CGT CTA CTG GAC CTC GGA TAT TAC CTT GAC CCT GCT CCA CGC
Val Lys Ala Asp Asp Leu Glu Pro Ile Met Glu Leu Gly Arg Gly Ala>

435         440         445         450         455         460         465         470         475         480
TAC GGG GTG GTG GAG AAG ATG CGG CAC GTG CCC AGC GGG CAG ATC ATG
ATG CCC CAC CAC CTC TTC TAC GCC GTG CAC GGG TCG CCC GTC TAG TAC
Tyr Gly Val Val Glu Lys Met Arg His Val Pro Ser Gly Gln Ile Met>

    485         490         495         500         505         510         515         520         525
GCA GTG AAG CGG ATC CGA GCC ACA GTA AAT AGC CAG GAA CAG AAA CGG
CGT CAC TTC GCC TAG GCT CGG TGT CAT TTA TCG GTC CTT GTC TTT GCC
Ala Val Lys Arg Ile Arg Ala Thr Val Asn Ser Gln Glu Gln Lys Arg>

530         535         540         545         550         555         560         565         570         575
CTA CTG ATG GAT TTG GAT ATT TCC ATG AGG ACG GTG GAC TGT CCA TTC
GAT GAC TAC CTA AAC CTA TAA AGG TAC TCC TGC CAC CTG ACA GGT AAG
```

FIG. 5A

```
Leu Leu Met Asp Leu Asp Ile Ser Met Arg Thr Val Asp Cys Pro Phe>

  580   585   590   595   600   605   610   615   620
ACT GTC ACC TTT TAT GGC GCA CTG TTT CGG GAG GGT GAT GTG TGG ATC
TGA CAG TGG AAA ATA CCG CGT GAC AAA GCC CTC CCA CTA CAC ACC TAG
Thr Val Thr Phe Tyr Gly Ala Leu Phe Arg Glu Gly Asp Val Trp Ile>

625   630   635   640   645   650   655   660   665   670
TGC ATG GAG CTC ATG GAT ACA TCA CTA GAT AAA TTC TAC AAA CAA GTT
ACG TAC CTC GAG TAC CTA TGT AGT GAT CTA TTT AAG ATG TTT GTT CAA
Cys Met Glu Leu Met Asp Thr Ser Leu Asp Lys Phe Tyr Lys Gln Val>

 675   680   685   690   695   700   705   710   715   720
ATT GAT AAA GGC CAG ACA ATT CCA GAG GAC ATC TTA GGG AAA ATA GCA
TAA CTA TTT CCG GTC TGT TAA GGT CTC CTG TAG AAT CCC TTT TAT CGT
Ile Asp Lys Gly Gln Thr Ile Pro Glu Asp Ile Leu Gly Lys Ile Ala>

   725   730   735   740   745   750   755   760   765
GTT TCT ATT GTA AAA GCA TTA GAA CAT TTA CAT AGT AAG CTG TCT GTC
CAA AGA TAA CAT TTT CGT AAT CTT GTA AAT GTA TCA TTC GAC AGA CAG
Val Ser Ile Val Lys Ala Leu Glu His Leu His Ser Lys Leu Ser Val>

770   775   780   785   790   795   800   805   810   815
ATT CAC AGA GAC GTC AAG CCT TCT AAT GTA CTC ATC AAT GCT CTC GGT
TAA GTG TCT CTG CAG TTC GGA AGA TTA CAT GAG TAG TTA CGA GAG CCA
Ile His Arg Asp Val Lys Pro Ser Asn Val Leu Ile Asn Ala Leu Gly>

  820   825   830   835   840   845   850   855   860
CAA GTG AAG ATG TGC GAT TTT GGA ATC AGT GGC TAC TTG GTG GAC TCT
GTT CAC TTC TAC ACG CTA AAA CCT TAG TCA CCG ATG AAC CAC CTG AGA
Gln Val Lys Met Cys Asp Phe Gly Ile Ser Gly Tyr Leu Val Asp Ser>

865   870   875   880   885   890   895   900   905   910
GTT GCT AAA ACA ATT GAT GCA GGT TGC AAA CCA TAC ATG GCC CCT GAA
CAA CGA TTT TGT TAA CTA CGT CCA ACG TTT GGT ATG TAC CGG GGA CTT
Val Ala Lys Thr Ile Asp Ala Gly Cys Lys Pro Tyr Met Ala Pro Glu>

915   920   925   930   935   940   945   950   955   960
AGA ATA AAC CCA GAG CTC AAC CAG AAG GGA TAC AGT GTG AAG TCT GAC
TCT TAT TTG GGT CTC GAG TTG GTC TTC CCT ATG TCA CAC TTC AGA CTG
Arg Ile Asn Pro Glu Leu Asn Gln Lys Gly Tyr Ser Val Lys Ser Asp>

   965   970   975   980   985   990   995   1000  1005
ATT TGG AGT CTG GGC ATC ACG ATG ATT GAG TTG GCC ATC CTT CGA TTT
TAA ACC TCA GAC CCG TAG TGC TAC TAA CTC AAC CGG TAG GAA GCT AAA
Ile Trp Ser Leu Gly Ile Thr Met Ile Glu Leu Ala Ile Leu Arg Phe>

1010  1015  1020  1025  1030  1035  1040  1045  1050  1055
CCC TAT GAT TCA TGG GGA ACT CCA TTT CAG CAG CTC AAA CAG GTG GTA
GGG ATA CTA AGT ACC CCT TGA GGT AAA GTC GTC GAG TTT GTC CAC CAT
Pro Tyr Asp Ser Trp Gly Thr Pro Phe Gln Gln Leu Lys Gln Val Val>
```

FIG. 5B

```
 1060  1065   1070   1075  1080   1085   1090  1095   1100
   *           *            *                  *           *
GAG GAG CCA TCG CCA CAA CTC CCA GCA GAC AAG TTC TCT GCA GAG TTT
CTC CTC GGT AGC GGT GTT GAG GGT CGT CTG TTC AAG AGA CGT CTC AAA
Glu Glu Pro Ser Pro Gln Leu Pro Ala Asp Lys Phe Ser Ala Glu Phe>

1105 1110   1115   1120  1125   1130   1135  1140   1145   1150
       *             *             *            *             *
GTT GAC TTT ACC TCA CAG TGC TTA AAG AAG AAT TCC AAA GAA CGG CCT
CAA CTG AAA TGG AGT GTC ACG AAT TTC TTC TTA AGG TTT CTT GCC GGA
Val Asp Phe Thr Ser Gln Cys Leu Lys Lys Asn Ser Lys Glu Arg Pro>

 1155   1160   1165  1170   1175   1180  1185   1190   1195  1200
          *            *             *            *             *
ACA TAC CCA GAG CTA ATG CAA CAT CCA TTT TTC ACC CTA CAT GAA TCC
TGT ATG GGT CTC GAT TAC GTT GTA GGT AAA AAG TGG GAT GTA CTT AGG
Thr Tyr Pro Glu Leu Met Gln His Pro Phe Phe Thr Leu His Glu Ser>

  1205   1210  1215   1220   1225  1230   1235   1240  1245  1250
           *             *             *            *          *
AAA GGA ACA GAT GTG GCA TCT TTT GTA AAA CTG ATT CTT GGA GAC TAAAA
TTT CCT TGT CTA CAC CGT AGA AAA CAT TTT GAC TAA GAA CCT CTG ATTTT
Lys Gly Thr Asp Val Ala Ser Phe Val Lys Leu Ile Leu Gly Asp> (SEQ ID NO:4)

 1255 1260   1265 1270   1275 1280   1285 1290   1295 1300   1305 1310
         *            *            *            *            *          *
AGCAGTGGAC TTAATCGGTT GACCCTACTG TGGATTGGTG GGTTTCGGGG TGAAGCAAGT
TCGTCACCTG AATTAGCCAA CTGGGATGAC ACCTAACCAC CCAAAGCCCC ACTTCGTTCA

 1315 1320   1325 1330   1335 1340   1345 1350   1355 1360   1365 1370
         *            *            *            *            *          *
TCACTACAGC ATCAATAGAA AGTCATCTTT GAGATAATTT AACCCTGCCT CTCAGAGGGT
AGTGATGTCG TAGTTATCTT TCAGTAGAAA CTCTATTAAA TTGGGACGGA GAGTCTCCCA

 1375 1380   1385 1390   1395 1400   1405 1410   1415 1420   1425 1430
         *            *            *            *            *          *
TTTCTCTCCC AATTTTCTTT TTACTCCCCC TCTTAAGGGG GCCTTGGAAT CTATAGTATA
AAAGAGAGGG TTAAAAGAAA AATGAGGGGG AGAATTCCCC CGGAACCTTA GATATCATAT

 1435 1440   1445 1450   1455 1460   1465 1470   1475 1480   1485 1490
         *            *            *            *            *          *
GAATGAACTG TCTAGATGGA TGAATTATGA TAAAGGCTTA GGACTTCAAA AGGTGATTAA
CTTACTTGAC AGATCTACCT ACTTAATACT ATTTCCGAAT CCTGAAGTTT TCCACTAATT

 1495 1500   1505 1510   1515 1520   1525 1530   1535 1540   1545 1550
         *            *            *            *            *          *
ATATTTAATG ATGTGTCATA TGAGTCCTCA AAAAAAAAAA AAAAAAAAAA AAAAAAAAAA
TATAAATTAC TACACAGTAT ACTCAGGAGT TTTTTTTTTT TTTTTTTTTT TTTTTTTTTT

 1555 1560   1565 1570   1575 1580   1585 1590   1595 1600
         *            *            *            *            *
AAAAAAAAAA AAAAAAAAAA AAAAAAAAAA AAAAAAAAAA AAAAAAAAAA AA  (SEQ ID NO:3)
TTTTTTTTTT TTTTTTTTTT TTTTTTTTTT TTTTTTTTTT TTTTTTTTTT TT
```

FIG. 5C

```
5         10        15        20        25        30        35        40        45        50        55
CTAGGGTCCC CGGCGCCAGG CCACCCGGCC GTCAGCAGC ATG CAG GGT AAA CGC AAA
GATCCCAGGG GCCGCGGTCC GGTGGGCCGG CAGTCGTCG TAC GTC CCA TTT GCG TTT
                                           Met Gln Gly Lys Arg Lys>

60  65  70  75  80  85  90  95  100  105
GCA CTG AAG TTG AAT TTT GCA AAT CCA CCT TTC AAA TCT ACA GCA AGG
CGT GAC TTC AAC TTA AAA CGT TTA GGT GGA AAG TTT AGA TGT CGT TCC
Ala Leu Lys Leu Asn Phe Ala Asn Pro Pro Phe Lys Ser Thr Ala Arg>

110  115  120  125  130  135  140  145  150
TTT ACT CTG AAT CCC AAT CCT ACA GGA GTT CAA AAC CCA CAC ATA GAG
AAA TGA GAC TTA GGG TTA GGA TGT CCT CAA GTT TTG GGT GTG TAT CTC
Phe Thr Leu Asn Pro Asn Pro Thr Gly Val Gln Asn Pro His Ile Glu>

155  160  165  170  175  180  185  190  195  200
AGA CTG AGA ACA CAC AGC ATT GAG TCA TCA GGA AAA CTG AAG ATC TCC
TCT GAC TCT TGT GTG TCG TAA CTC AGT AGT CCT TTT GAC TTC TAG AGG
Arg Leu Arg Thr His Ser Ile Glu Ser Ser Gly Lys Leu Lys Ile Ser>

205  210  215  220  225  230  235  240  245
CCT GAA CAA CAC TGG GAT TTC ACT GCA GAG GAC TTG AAA GAC CTT GGA
GGA CTT GTT GTG ACC CTA AAG TGA CGT CTC CTG AAC TTT CTG GAA CCT
Pro Glu Gln His Trp Asp Phe Thr Ala Glu Asp Leu Lys Asp Leu Gly>

250  255  260  265  270  275  280  285  290  295
GAA ATT GGA CGA GGA GCT TAT GGT TCT GTC AAC AAA ATG GTC CAC AAA
CTT TAA CCT GCT CCT CGA ATA CCA AGA CAG TTG TTT TAC CAG GTG TTT
Glu Ile Gly Arg Gly Ala Tyr Gly Ser Val Asn Lys Met Val His Lys>

300  305  310  315  320  325  330  335  340  345
CCA AGT GGG CAA ATA ATG GCA GTT AAA AGA ATT CGG TCA ACA GTG GAT
GGT TCA CCC GTT TAT TAC CGT CAA TTT TCT TAA GCC AGT TGT CAC CTA
Pro Ser Gly Gln Ile Met Ala Val Lys Arg Ile Arg Ser Thr Val Asp>

350  355  360  365  370  375  380  385  390
GAA AAA GAA CAA AAA CAA CTT CTT ATG GAT TTG GAT GTA GTA ATG CGG
CTT TTT CTT GTT TTT GTT GAA GAA TAC CTA AAC CTA CAT CAT TAC GCC
Glu Lys Glu Gln Lys Gln Leu Leu Met Asp Leu Asp Val Val Met Arg>

395  400  405  410  415  420  425  430  435  440
AGT AGT GAT TGC CCA TAC ATT GTT CAG TTT TAT GGT GCA CTC TTC AGA
TCA TCA CTA ACG GGT ATG TAA CAA GTC AAA ATA CCA CGT GAG AAG TCT
Ser Ser Asp Cys Pro Tyr Ile Val Gln Phe Tyr Gly Ala Leu Phe Arg>

445  450  455  460  465  470  475  480  485
GAG GGT GAC TGT TGG ATC TGT ATG GAA CTC ATG TCT ACC TCG TTT GAT
CTC CCA CTG ACA ACC TAG ACA TAC CTT GAG TAC AGA TGG AGC AAA CTA
Glu Gly Asp Cys Trp Ile Cys Met Glu Leu Met Ser Thr Ser Phe Asp>
```

FIG. 6A

```
490 495 500 505 510 515 520 525 530 535
AAG TTT TAC AAA TAT GTA TAT AGT GTA TTA GAT GAT GTT ATT CCA GAA
TTC AAA ATG TTT ATA CAT ATA TCA CAT AAT CTA CTA CAA TAA GGT CTT
Lys Phe Tyr Lys Tyr Val Tyr Ser Val Leu Asp Asp Val Ile Pro Glu>

540 545 550 555 560 565 570 575 580 585
GAA ATT TTA GGC AAA ATC ACT TTA GCA ACT GTG AAA GCA CTA AAC CAC
CTT TAA AAT CCG TTT TAG TGA AAT CGT TGA CAC TTT CGT GAT TTG GTG
Glu Ile Leu Gly Lys Ile Thr Leu Ala Thr Val Lys Ala Leu Asn His>

590 595 600 605 610 615 620 625 630
TTA AAA GAA AAC TTG AAA ATT ATT CAC AGA GAT ATC AAA CCT TCC AAT
AAT TTT CTT TTG AAC TTT TAA TAA GTG TCT CTA TAG TTT GGA AGG TTA
Leu Lys Glu Asn Leu Lys Ile Ile His Arg Asp Ile Lys Pro Ser Asn>

635 640 645 650 655 660 665 670 675 680
ATT CTT CTG GAC AGA AGT GGA AAT ATT AAG CTC TGT GAC TTC GGC ATC
TAA GAA GAC CTG TCT TCA CCT TTA TAA TTC GAG ACA CTG AAG CCG TAG
Ile Leu Leu Asp Arg Ser Gly Asn Ile Lys Leu Cys Asp Phe Gly Ile>

685 690 695 700 705 710 715 720 725
AGT GGA CAG CTT GTG GAC TCT ATT GCC AAG ACA AGA GAT GCT GGC TGT
TCA CCT GTC GAA CAC CTG AGA TAA CGG TTC TGT TCT CTA CGA CCG ACA
Ser Gly Gln Leu Val Asp Ser Ile Ala Lys Thr Arg Asp Ala Gly Cys>

730 735 740 745 750 755 760 765 770 775
AGG CCA TAC ATG GCA CCT GAA AGA ATA GAC CCA AGC GCA TCA CGA CAA
TCC GGT ATG TAC CGT GGA CTT TCT TAT CTG GGT TCG CGT AGT GCT GTT
Arg Pro Tyr Met Ala Pro Glu Arg Ile Asp Pro Ser Ala Ser Arg Gln>

780 785 790 795 800 805 810 815 820 825
GGA TAT GAT GTC CGC TCT GAT GTC TGG AGT TTG GGG ATC ACA TTG TAT
CCT ATA CTA CAG GCG AGA CTA CAG ACC TCA AAC CCC TAG TGT AAC ATA
Gly Tyr Asp Val Arg Ser Asp Val Trp Ser Leu Gly Ile Thr Leu Tyr>

830 835 840 845 850 855 860 865 870
GAG TTG GCC ACA GGC CGA TTT CCT TAT CCA AAG TGG AAT AGT GTA TTT
CTC AAC CGG TGT CCG GCT AAA GGA ATA GGT TTC ACC TTA TCA CAT AAA
Glu Leu Ala Thr Gly Arg Phe Pro Tyr Pro Lys Trp Asn Ser Val Phe>

875 880 885 890 895 900 905 910 915 920
GAT CAA CTA ACA CAA GTC GTG AAA GGA GAT CCT CCG CAG CTG AGT AAT
CTA GTT GAT TGT GTT CAG CAC TTT CCT CTA GGA GGC GTC GAC TCA TTA
Asp Gln Leu Thr Gln Val Val Lys Gly Asp Pro Pro Gln Leu Ser Asn>

925 930 935 940 945 950 955 960 965
TCT GAG GAA AGG GAA TTC TCC CCG AGT TTC ATC AAC TTT GTC AAC TTG
AGA CTC CTT TCC CTT AAG AGG GGC TCA AAG TAG TTG AAA CAG TTG AAC
Ser Glu Glu Arg Glu Phe Ser Pro Ser Phe Ile Asn Phe Val Asn Leu>

970 975 980 985 990 995 1000 1005 1010 1015
```

FIG. 6B

```
TGC CTT ACG AAG GAT GAA TCC AAA AGG CCA AAG TAT AAA GAG CTT CTG
ACG GAA TGC TTC CTA CTT AGG TTT TCC GGT TTC ATA TTT CTC GAA GAC
Cys Leu Thr Lys Asp Glu Ser Lys Arg Pro Lys Tyr Lys Glu Leu Leu>

1020   1025   1030  1035   1040   1045  1050   1055   1060  1065
AAA CAT CCC TTT ATT TTG ATG TAT GAA GAA CGT GCC GTT GAG GTC GCA
TTT GTA GGG AAA TAA AAC TAC ATA CTT CTT GCA CGG CAA CTC CAG CGT
Lys His Pro Phe Ile Leu Met Tyr Glu Glu Arg Ala Val Glu Val Ala>

  1070   1075  1080   1085   1090  1095   1100   1105  1110
TGC TAT GTT TGT AAA ATC CTG GAT CAA ATG CCA GCT ACT CCC AGC TCT
ACG ATA CAA ACA TTT TAG GAC CTA GTT TAC GGT CGA TGA GGG TCG AGA
Cys Tyr Val Cys Lys Ile Leu Asp Gln Met Pro Ala Thr Pro Ser Ser>

1115   1120  1125   1130  1135 1140  1145 1150  1155 1160  1165 1170
CCC ATG TAT GTC GAT TG ATATCGYTGC TACATCAGAC TCTAGAAAAA AGGGCTGAGA
GGG TAC ATA CAG CTA AC TATAGCRACG ATGTAGTCTG AGATCTTTTT TCCCGACTCT
Pro Met Tyr Val Asp>  (SEQ ID NO:6)

 1175 1180  1185 1190  1195 1200  1205 1210  1215 1220  1225 1230
GGAAGCAAGA CGTAAAGAAT TTTCATCCCG TATCACAGTG TTTTTATTGC TCGCCCAGAC
CCTTCGTTCT GCATTTCTTA AAAGTAGGGC ATAGTGTCAC AAAAATAACG AGCGGGTCTG

 1235 1240  1245 1250  1255 1260  1265 1270  1275 1280  1285 1290
ACCATGTGCA ATAAGATTGG TGTTCGTTTC CATCATGTCT GTATACTCCT GTCACCTAGA
TGGTACACGT TATTCTAACC ACAAGCAAAG GTAGTACAGA CATATGAGGA CAGTGGATCT

 1295 1300  1305 1310  1315 1320  1325 1330  1335 1340  1345 1350
ACGTGCATCC TTGTAATACC TGATTGATCA CACAGTGTTA GTGCTGGTCA GAGAGACCTC
TGCACGTAGG AACATTATGG ACTAACTAGT GTGTCACAAT CACGACCAGT CTCTCTGGAG

 1355 1360  1365 1370  1375 1380  1385 1390  1395 1400  1405 1410
ATCCTGCTCT TTTGTGATGA ACATATTCAT GAAATGTGGA AGTCAGTACG ATCAAGTTGT
TAGGACGAGA AAACACTACT TGTATAAGTA CTTTACACCT TCAGTCATGC TAGTTCAACA

 1415 1420  1425 1430  1435 1440  1445 1450  1455 1460  1465 1470
TGACTGTGAT TAGATCACAT CTTAAATTCA TTTCTAGACT CAAAACCTGG AGATGCAGCT
ACTGACACTA ATCTAGTGTA GAATTTAAGT AAAGATCTGA GTTTTGGACC TCTACGTCGA

 1475 1480  1485 1490  1495 1500  1505 1510  1515 1520  1525 1530
ACTGGAATGG TGTTTTGTCA GACTTCCAAA TCCTGGAAGG ACACAGTGAT GAATGTACTA
TGACCTTACC ACAAAACAGT CTGAAGGTTT AGGACCTTCC TGTGTCACTA CTTACATGAT

 1535 1540  1545 1550  1555 1560  1565 1570  1575 1580  1585 1590
TATCTGAACA TAGAAACTCG GGCTTGAGTG AGAAGAGCTT GCACAGCCAA CGAGACACAT
ATAGACTTGT ATCTTTGAGC CCGAACTCAC TCTTCTCGAA CGTGTCGGTT GCTCTGTGTA

 1595 1600  1605 1610  1615 1620  1625 1630  1635 1640  1645 1650
TGCCTTCTGG AGCTGGGAGA CAAAGGAGGA ATTTACTTTC TTCACCAAGT GCAATAGATT
ACGGAAGACC TCGACCCTCT GTTTCCTCCT TAAATGAAAG AAGTGGTTCA CGTTATCTAA
```

FIG. 6C

```
 1655 1660  1665 1670  1675 1680  1685 1690  1695 1700  1705 1710
         *          *          *          *          *          *
ACTGATGTGA TATTCTGTTG CTTTACAGTT ACAGTTGATG TTTGGGGATC GATGTGCTCA
TGACTACACT ATAAGACAAC GAAATGTCAA TGTCAACTAC AAACCCCTAG CTACACGAGT

 1715 1720  1725 1730  1735 1740  1745 1750  1755 1760  1765 1770
         *          *          *          *          *          *
GCCAAATTTC CTGTTTGAAA TATCATGTTA AATTAGAATG AATTTATCTT TACCAAAAAC
CGGTTTAAAG GACAAACTTT ATAGTACAAT TTAATCTTAC TTAAATAGAA ATGGTTTTTG

 1775 1780  1785 1790  1795 1800  1805 1810  1815 1820  1825 1830
         *          *          *          *          *          *
CATGTTGCGT TCAAAGAGGT GAACATTAAA ATATAGAGAC AGGACAGAAT GTGTTCTTTT
GTACAACGCA AGTTTCTCCA CTTGTAATTT TATATCTCTG TCCTGTCTTA CACAAGAAAA

 1835 1840  1845 1850  1855 1860  1865 1870  1875 1880  1885 1890
         *          *          *          *          *          *
CTCCTCTACC AGTCCTATTT TTCAATGGGA AGACTCAGGA GTCTGCCACT TGTCAAAGAA
GAGGAGATGG TCAGGATAAA AAGTTACCCT TCTGAGTCCT CAGACGGTGA ACAGTTTCTT

 1895 1900  1905 1910  1915 1920  1925 1930  1935 1940  1945 1950
         *          *          *          *          *          *
GGTGCTGATC CTAAGAATTT TTCATTCTCA GAATTCGGTG TGCTGCCAAC TTGATGTTCC
CCACGACTAG GATTCTTAAA AAGTAAGAGT CTTAAGCCAC ACGACGGTTG AACTACAAGG

 1955 1960  1965 1970  1975 1980  1985 1990  1995 2000  2005 2010
         *          *          *          *          *          *
ACCTGCCACA AACCACCAGG ACTGAAAGAA GAAAACAGTA CAGAAGGCAA AGTTTACAGA
TGGACGGTGT TTGGTGGTCC TGACTTTCTT CTTTTGTCAT GTCTTCCGTT TCAAATGTCT

 2015 2020  2025 2030  2035 2040  2045 2050  2055 2060  2065 2070
         *          *          *          *          *          *
TGTTTTTAAT TCTAGTATTT TATCTGGAAC AACTTGTAGC AGCTATATAT TTCCCCTTGG
ACAAAAATTA AGATCATAAA ATAGACCTTG TTGAACATCG TCGATATATA AAGGGGAACC

 2075 2080  2085 2090  2095 2100  2105 2110  2115 2120  2125 2130
         *          *          *          *          *          *
TCCCAAGCCT GATACTTTAG CCATCATAAC TCACTAACAG GGAGAAGTAG CTAGTAGCAA
AGGGTTCGGA CTATGAAATC GGTAGTATTG AGTGATTGTC CCTCTTCATC GATCATCGTT

 2135 2140  2145 2150  2155 2160  2165 2170  2175 2180  2185 2190
         *          *          *          *          *          *
TGTGCCTTGA TTGATTAGAT AAAGATTTCT AGTAGGCAGC AAAAGACCAA ATCTCAGTTG
ACACGGAACT AACTAATCTA TTTCTAAAGA TCATCCGTCG TTTTCTGGTT TAGAGTCAAC

 2195 2200  2205 2210  2215 2220  2225 2230  2235 2240  2245 2250
         *          *          *          *          *          *
TTTGCTTCTT GCCATCACTG GTCCAGGTCT TCAGTTTCCG AATCTCTTTC CCTTCCCCTG
AAACGAAGAA CGGTAGTGAC CAGGTCCAGA AGTCAAAGGC TTAGAGAAAG GGAAGGGGAC

 2255 2260  2265 2270  2275 2280  2285 2290  2295 2300  2305 2310
         *          *          *          *          *          *
TGGTCTATTG TCGCTATGTG ACTTGCGCTT AATCCAATAT TTTGCCTTTT TTCTATATCA
ACCAGATAAC AGCGATACAC TGAACGCGAA TTAGGTTATA AAACGGAAAA AAGATATAGT

 2315 2320  2325 2330  2335 2340  2345 2350  2355 2360  2365 2370
         *          *          *          *          *          *
AAAAACCTTT ACAGTTAGCA GGGATGTTCC TTACCGAGGA TTTTTAACCC CCAATCTCTC
TTTTTGGAAA TGTCAATCGT CCCTACAAGG AATGGCTCCT AAAAATTGGG GGTTAGAGAG

 2375 2380  2385 2390  2395 2400  2405 2410  2415 2420  2425 2430
         *          *          *          *          *          *
```

FIG. 6D

```
ATAATCGCTA GTGTTTAAAA GGCTAAGAAT AGTGGGGCCC AACCGATGTG GTAGGTGATA
TATTAGCGAT CACAAATTTT CCGATTCTTA TCACCCCGGG TTGGCTACAC CATCCACTAT

 2435 2440  2445 2450  2455 2460  2465 2470  2475 2480  2485 2490
         *          *          *          *          *          *
AAGAGGCATC TTTTCTAGAG ACACATTGGA CCAGATGAGG ATCCGAAACG GCAGCCTTTA
TTCTCCGTAG AAAAGATCTC TGTGTAACCT GGTCTACTCC TAGGCTTTGC CGTCGGAAAT

 2495 2500  2505 2510  2515 2520  2525 2530  2535 2540  2545 2550
         *          *          *          *          *          *
CGTTCATCAC CTGCTAGAAC CTCTCGTAGT CCATCACCAT TTCTTGGCAT TGGAATTCTA
GCAAGTAGTG GACGATCTTG GAGAGCATCA GGTAGTGGTA AAGAACCGTA ACCTTAAGAT

 2555 2560  2565 2570  2575 2580  2585 2590  2595 2600  2605 2610
         *          *          *          *          *          *
CTGGAAAAAA ATACAAAAAG CAAAACAAAA CCCTCAGCAC TGTTACAAGA GGCCATTTAA
GACCTTTTTT TATGTTTTTC GTTTTGTTTT GGGAGTCGTG ACAATGTTCT CCGGTAAATT

 2615 2620  2625 2630  2635 2640  2645 2650  2655 2660  2665 2670
         *          *          *          *          *          *
GTATCTTGTG CTTCTTCACT TACCCATTAG CCAGGTTCTC ATTAGGTTTT GCTTGGGCCT
CATAGAACAC GAAGAAGTGA ATGGGTAATC GGTCCAAGAG TAATCCAAAA CGAACCCGGA

 2675 2680  2685 2690  2695 2700  2705 2710  2715 2720  2725 2730
         *          *          *          *          *          *
CCCTGGCACT GAACCTTAGG CTTTGTATGA CAGTGAAGCA GCACTGTGAG TGGTTCAAGC
GGGACCGTGA CTTGGAATCC GAAACATACT GTCACTTCGT CGTGACACTC ACCAAGTTCG

 2735 2740  2745 2750  2755 2760  2765 2770  2775 2780  2785 2790
         *          *          *          *          *          *
ACACTGGAAT ATAAAACAGT CATGGCCTGA GATGCAGGTG ATGCCATTAC AGAACCAAAT
TGTGACCTTA TATTTTGTCA GTACCGGACT CTACGTCCAC TACGGTAATG TCTTGGTTTA

 2795 2800  2805 2810  2815 2820  2825 2830  2835 2840  2845 2850
         *          *          *          *          *          *
CGTGGCACGT ATTGCTGTGT CTCCTCTCAG AGTGACAGTC ATAAATACTG TCAAACAATA
GCACCGTGCA TAACGACACA GAGGAGAGTC TCACTGTCAG TATTTATGAC AGTTTGTTAT

 2855 2860  2865 2870  2875 2880  2885 2890  2895 2900  2905 2910
         *          *          *          *          *          *
AAGGGAGAAT GGTGCTGTTT AAAGTCACAT CCCTGTAAAT TGCAGAATTC AAAAGTGATT
TTCCCTCTTA CCACGACAAA TTTCAGTGTA GGGACATTTA ACGTCTTAAG TTTTCACTAA

 2915 2920  2925 2930  2935 2940  2945 2950  2955 2960  2965 2970
         *          *          *          *          *          *
ATCTCTTTGA TCTACTTGCC TCATTTCCCT ATCTTCTCCC CCACGGTATC CTAAACTTTA
TAGAGAAACT AGATGAACGG AGTAAAGGGA TAGAAGAGGG GGTGCCATAG GATTTGAAAT

 2975 2980  2985 2990  2995 3000  3005 3010  3015 3020  3025 3030
         *          *          *          *          *          *
GACTTCCCAC TGTTCTGAAA GGAGACATTG CTCTATGTCT GCCTTCGACC ACAGCAAGCC
CTGAAGGGTG ACAAGACTTT CCTCTGTAAC GAGATACAGA CGGAAGCTGG TGTCGTTCGG

 3035 3040  3045 3050  3055 3060  3065 3070  3075 3080  3085 3090
         *          *          *          *          *          *
ATCATCCTCC ATTGCTCCCG GGGACTCAAG AGGAATCTGT TTCTCTGCTG TCAACTTCCC
TAGTAGGAGG TAACGAGGGC CCCTGAGTTC TCCTTAGACA AAGAGACGAC AGTTGAAGGG

 3095 3100  3105 3110  3115 3120  3125 3130  3135 3140  3145 3150
         *          *          *          *          *          *
ATCTGGCTCA GCATAGGGTC ACTTTGCCAT TATGCAAATG GAGATAAAAG CAATTCTGGC
TAGACCGAGT CGTATCCCAG TGAAACGGTA ATACGTTTAC CTCTATTTTC GTTAAGACCG
```

FIG. 6E

```
 3155 3160  3165 3170  3175 3180  3185 3190  3195 3200  3205 3210
         *          *          *          *          *          *
TGTCCAGGAG CTAATCTGAC CGTTCTATTG TGTGGATGAC CACATAAGAA GGCAATTTTA
ACAGGTCCTC GATTAGACTG GCAAGATAAC ACACCTACTG GTGTATTCTT CCGTTAAAAT

 3215 3220  3225 3230  3235 3240  3245 3250  3255 3260  3265 3270
         *          *          *          *          *          *
GTGTATTAAT CATAGATTAT TATAAACTAT AAACTTAAGG GCAAGGAGTT TATTACAATG
CACATAATTA GTATCTAATA ATATTTGATA TTTGAATTCC CGTTCCTCAA ATAATGTTAC

 3275 3280  3285 3290  3295 3300  3305 3310  3315 3320  3325 3330
         *          *          *          *          *          *
TATCTTTATT AAAACAAAAG GGTGTATAGT GTTCACAAAC TGTGAAAATA GTGTAAGAAC
ATAGAAATAA TTTTGTTTTC CCACATATCA CAAGTGTTTG ACACTTTTAT CACATTCTTG

 3335 3340  3345 3350  3355 3360  3365 3370  3375 3380  3385 3390
         *          *          *          *          *          *
TGTACATTGT GAGCTCTGGT TATTTTTCTC TTGTACCATA GAAAAATGTA TAAAAATTAT
ACATGTAACA CTCGAGACCA ATAAAAAGAG AACATGGTAT CTTTTTACAT ATTTTTAATA

 3395 3400  3405 3410  3415 3420  3425 3430  3435 3440  3445 3450
         *          *          *          *          *          *
CAAAAAGCTA ATGTGCAGGG ATATTGCCTT ATTTGTCTGT AAAAAATGGA GCTCAGTAAC
GTTTTTCGAT TACACGTCCC TATAACGGAA TAAACAGACA TTTTTTACCT CGAGTCATTG

 3455 3460  3465 3470  3475 3480  3485 3490  3495
         *          *          *          *
ATAACTGCTT CTTGGAGCTT TGGAATATTT TATCCTGTAT TCTTGTTT  (SEQ ID NO:5)
TATTGACGAA GAACCTCGAA ACCTTATAAA ATAGGACATA AGAACAAA
```

FIG. 6F

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      5         10         15         20         25         30         35         40         45         50
CAACA ATG GCG GCT CCG AGC CCG AGC GGT GGC GGC GGC AGC GGC ACC CCC
GTTGT TAC CGC CGA GGC TCG GGC TCG CCA CCG CCG CCG TCG CCG TGG GGG
      Met Ala Ala Pro Ser Pro Ser Gly Gly Gly Gly Ser Gly Thr Pro>

      55         60         65         70         75         80         85         90         95
GGC CCC GTA GGG TCC CCG GCG CCA GGC CAC CCG GCC GTC AGC AGC ATG
CCG GGG CAT CCC AGG GGC CGC GGT CCG GTG GGC CGG CAG TCG TCG TAC
Gly Pro Val Gly Ser Pro Ala Pro Gly His Pro Ala Val Ser Ser Met>

100         105         110         115         120         125         130         135         140         145
CAG GGT AAA CGC AAA GCA CTG AAG TTG AAT TTT GCA AAT CCA CCT TTC
GTC CCA TTT GCG TTT CGT GAC TTC AAC TTA AAA CGT TTA GGT GGA AAG
Gln Gly Lys Arg Lys Ala Leu Lys Leu Asn Phe Ala Asn Pro Pro Phe>

    150         155         160         165         170         175         180         185         190
AAA TCT ACA GCA AGG TTT ACT CTG AAT CCC AAT CCT ACA GGA GTT CAA
TTT AGA TGT CGT TCC AAA TGA GAC TTA GGG TTA GGA TGT CCT CAA GTT
Lys Ser Thr Ala Arg Phe Thr Leu Asn Pro Asn Pro Thr Gly Val Gln>

195         200         205         210         215         220         225         230         235         240
AAC CCA CAC ATA GAG AGA CTG AGA ACA CAC AGC ATT GAG TCA TCA GGA
TTG GGT GTG TAT CTC TCT GAC TCT TGT GTG TCG TAA CTC AGT AGT CCT
Asn Pro His Ile Glu Arg Leu Arg Thr His Ser Ile Glu Ser Ser Gly>

245         250         255         260         265         270         275         280         285         290
AAA CTG AAG ATC TCC CCT GAA CAA CAC TGG GAT TTC ACT GCA GAG GAC
TTT GAC TTC TAG AGG GGA CTT GTT GTG ACC CTA AAG TGA CGT CTC CTG
Lys Leu Lys Ile Ser Pro Glu Gln His Trp Asp Phe Thr Ala Glu Asp>

    295         300         305         310         315         320         325         330         335
TTG AAA GAC CTT GGA GAA ATT GGA CGA GGA GCT TAT GGT TCT GTC AAC
AAC TTT CTG GAA CCT CTT TAA CCT GCT CCT CGA ATA CCA AGA CAG TTG
Leu Lys Asp Leu Gly Glu Ile Gly Arg Gly Ala Tyr Gly Ser Val Asn>

340         345         350         355         360         365         370         375         380         385
AAA ATG GTC CAC AAA CCA AGT GGG CAA ATA ATG GCA GTT AAA AGA ATT
TTT TAC CAG GTG TTT GGT TCA CCC GTT TAT TAC CGT CAA TTT TCT TAA
Lys Met Val His Lys Pro Ser Gly Gln Ile Met Ala Val Lys Arg Ile>

    390         395         400         405         410         415         420         425         430
CGG TCA ACA GTG GAT GAA AAA GAA CAA AAA CAA CTT CTT ATG GAT TTG
GCC AGT TGT CAC CTA CTT TTT CTT GTT TTT GTT GAA GAA TAC CTA AAC
Arg Ser Thr Val Asp Glu Lys Glu Gln Lys Gln Leu Leu Met Asp Leu>

435         440         445         450         455         460         465         470         475         480
GAT GTA GTA ATG CGG AGT AGT GAT TGC CCA TAC ATT GTT CAG TTT TAT
CTA CAT CAT TAC GCC TCA TCA CTA ACG GGT ATG TAA CAA GTC AAA ATA
Asp Val Val Met Arg Ser Ser Asp Cys Pro Tyr Ile Val Gln Phe Tyr>
```

FIG. 7A

19/54

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485  490  495  500  505  510  515  520  525  530
GGT GCA CTC TTC AGA GAG GGT GAC TGT TGG ATC TGT ATG GAA CTC ATG
CCA CGT GAG AAG TCT CTC CCA CTG ACA ACC TAG ACA TAC CTT GAG TAC
Gly Ala Leu Phe Arg Glu Gly Asp Cys Trp Ile Cys Met Glu Leu Met>

535  540  545  550  555  560  565  570  575
TCT ACC TCG TTT GAT AAG TTT TAC AAA TAT GTA TAT AGT GTA TTA GAT
AGA TGG AGC AAA CTA TTC AAA ATG TTT ATA CAT ATA TCA CAT AAT CTA
Ser Thr Ser Phe Asp Lys Phe Tyr Lys Tyr Val Tyr Ser Val Leu Asp>

580  585  590  595  600  605  610  615  620  625
GAT GTT ATT CCA GAA GAA ATT TTA GGC AAA ATC ACT TTA GCA ACT GTG
CTA CAA TAA GGT CTT CTT TAA AAT CCG TTT TAG TGA AAT CGT TGA CAC
Asp Val Ile Pro Glu Glu Ile Leu Gly Lys Ile Thr Leu Ala Thr Val>

630  635  640  645  650  655  660  665  670
AAA GCA CTA AAC CAC TTA AAA GAA AAC TTG AAA ATT ATT CAC AGA GAT
TTT CGT GAT TTG GTG AAT TTT CTT TTG AAC TTT TAA TAA GTG TCT CTA
Lys Ala Leu Asn His Leu Lys Glu Asn Leu Lys Ile Ile His Arg Asp>

675  680  685  690  695  700  705  710  715  720
ATC AAA CCT TCC AAT ATT CTT CTG GAC AGA AGT GGA AAT ATT AAG CTC
TAG TTT GGA AGG TTA TAA GAA GAC CTG TCT TCA CCT TTA TAA TTC GAG
Ile Lys Pro Ser Asn Ile Leu Leu Asp Arg Ser Gly Asn Ile Lys Leu>

725  730  735  740  745  750  755  760  765  770
TGT GAC TTC GGC ATC AGT GGA CAG CTT GTG GAC TCT ATT GCC AAG ACA
ACA CTG AAG CCG TAG TCA CCT GTC GAA CAC CTG AGA TAA CGG TTC TGT
Cys Asp Phe Gly Ile Ser Gly Gln Leu Val Asp Ser Ile Ala Lys Thr>

775  780  785  790  795  800  805  810  815
AGA GAT GCT GGC TGT AGG CCA TAC ATG GCA CCT GAA AGA ATA GAC CCA
TCT CTA CGA CCG ACA TCC GGT ATG TAC CGT GGA CTT TCT TAT CTG GGT
Arg Asp Ala Gly Cys Arg Pro Tyr Met Ala Pro Glu Arg Ile Asp Pro>

820  825  830  835  840  845  850  855  860  865
AGC GCA TCA CGA CAA GGA TAT GAT GTC CGC TCT GAT GTC TGG AGT TTG
TCG CGT AGT GCT GTT CCT ATA CTA CAG GCG AGA CTA CAG ACC TCA AAC
Ser Ala Ser Arg Gln Gly Tyr Asp Val Arg Ser Asp Val Trp Ser Leu>

870  875  880  885  890  895  900  905  910
GGG ATC ACA TTG TAT GAG TTG GCC ACA GGC CGA TTT CCT TAT CCA AAG
CCC TAG TGT AAC ATA CTC AAC CGG TGT CCG GCT AAA GGA ATA GGT TTC
Gly Ile Thr Leu Tyr Glu Leu Ala Thr Gly Arg Phe Pro Tyr Pro Lys>

915  920  925  930  935  940  945  950  955  960
TGG AAT AGT GTA TTT GAT CAA CTA ACA CAA GTC GTG AAA GGA GAT CCT
ACC TTA TCA CAT AAA CTA GTT GAT TGT GTT CAG CAC TTT CCT CTA GGA
Trp Asn Ser Val Phe Asp Gln Leu Thr Gln Val Val Lys Gly Asp Pro>

965  970  975  980  985  990  995  1000  1005  1010
```

FIG. 7B

```
CCG CAG CTG AGT AAT TCT GAG GAA AGG GAA TTC TCC CCG AGT TTC ATC
GGC GTC GAC TCA TTA AGA CTC CTT TCC CTT AAG AGG GGC TCA AAG TAG
Pro Gln Leu Ser Asn Ser Glu Glu Arg Glu Phe Ser Pro Ser Phe Ile>

  1015   1020  1025   1030   1035  1040   1045   1050  1055
           *             *             *              *

AAC TTT GTC AAC TTG TGC CTT ACG AAG GAT GAA TCC AAA AGG CCA AAG
TTG AAA CAG TTG AAC ACG GAA TGC TTC CTA CTT AGG TTT TCC GGT TTC
Asn Phe Val Asn Leu Cys Leu Thr Lys Asp Glu Ser Lys Arg Pro Lys>

1060   1065  1070   1075   1080  1085   1090   1095  1100   1105
  *            *             *             *              *

TAT AAA GAG CTT CTG AAA CAT CCC TTT ATT TTG ATG TAT GAA GAA CGT
ATA TTT CTC GAA GAC TTT GTA GGG AAA TAA AAC TAC ATA CTT CTT GCA
Tyr Lys Glu Leu Leu Lys His Pro Phe Ile Leu Met Tyr Glu Glu Arg>

 1110  1115   1120   1125  1130   1135   1140  1145   1150
   *            *            *              *             *

GCC GTT GAG GTC GCA TGC TAT GTT TGT AAA ATC CTG GAT CAA ATG CCA
CGG CAA CTC CAG CGT ACG ATA CAA ACA TTT TAG GAC CTA GTT TAC GGT
Ala Val Glu Val Ala Cys Tyr Val Cys Lys Ile Leu Asp Gln Met Pro>

1155  1160   1165   1170  1175   1180   1185 1190  1195 1200
        *             *            *            *          *

GCT ACT CCC AGC TCT CCC ATG TAT GTC GAT TGATAT CGYTGCTACA
CGA TGA GGG TCG AGA GGG TAC ATA CAG CTA ACTATA GCRACGATGT
Ala Thr Pro Ser Ser Pro Met Tyr Val Asp> (SEQ ID NO:8)

 1205 1210   1215 1220   1225 1230   1235 1240   1245 1250   1255 1260
         *           *           *           *           *           *

TCAGACTCTA GAAAAAAGGG CTGAGAGGAA GCAAGACGTA AAGAATTTTC ATCCCGTATC
AGTCTGAGAT CTTTTTTCCC GACTCTCCTT CGTTCTGCAT TTCTTAAAAG TAGGGCATAG

 1265 1270   1275 1280   1285 1290   1295 1300   1305 1310   1315 1320
         *           *           *           *           *           *

ACAGTGTTTT TATTGCTCGC CCAGACACCA TGTGCAATAA GATTGGTGTT CGTTTCCATC
TGTCACAAAA ATAACGAGCG GGTCTGTGGT ACACGTTATT CTAACCACAA GCAAAGGTAG

 1325 1330   1335 1340   1345 1350   1355 1360   1365 1370   1375 1380
         *           *           *           *           *           *

ATGTCTGTAT ACTCCTGTCA CCTAGAACGT GCATCCTTGT AATACCTGAT TGATCACACA
TACAGACATA TGAGGACAGT GGATCTTGCA CGTAGGAACA TTATGGACTA ACTAGTGTGT

 1385 1390   1395 1400   1405 1410   1415 1420   1425 1430   1435 1440
         *           *           *           *           *           *

GTGTTAGTGC TGGTCAGAGA GACCTCATCC TGCTCTTTTG TGATGAACAT ATTCATGAAA
CACAATCACG ACCAGTCTCT CTGGAGTAGG ACGAGAAAAC ACTACTTGTA TAAGTACTTT

 1445 1450   1455 1460   1465 1470   1475 1480   1485 1490   1495 1500
         *           *           *           *           *           *

TGTGGAAGTC AGTACGATCA AGTTGTTGAC TGTGATTAGA TCACATCTTA AATTCATTTC
ACACCTTCAG TCATGCTAGT TCAACAACTG ACACTAATCT AGTGTAGAAT TTAAGTAAAG

 1505 1510   1515 1520   1525 1530   1535 1540   1545 1550   1555 1560
         *           *           *           *           *           *

TAGACTCAAA ACCTGGAGAT GCAGCTACTG GAATGGTGTT TTGTCAGACT TCCAAATCCT
ATCTGAGTTT TGGACCTCTA CGTCGATGAC CTTACCACAA AACAGTCTGA AGGTTTAGGA

 1565 1570   1575 1580   1585 1590   1595 1600   1605 1610   1615 1620
         *           *           *           *           *           *

GGAAGGACAC AGTGATGAAT GTACTATATC TGAACATAGA AACTCGGGCT TGAGTGAGAA
CCTTCCTGTG TCACTACTTA CATGATATAG ACTTGTATCT TTGAGCCCGA ACTCACTCTT
```

FIG. 7C

```
1625 1630  1635 1640  1645 1650  1655 1660  1665 1670  1675 1680
        *          *          *          *          *          *
GAGCTTGCAC AGCCAACGAG ACACATTGCC TTCTGGAGCT GGGAGACAAA GGAGGAATTT
CTCGAACGTG TCGGTTGCTC TGTGTAACGG AAGACCTCGA CCCTCTGTTT CCTCCTTAAA

1685 1690  1695 1700  1705 1710  1715 1720  1725 1730  1735 1740
        *          *          *          *          *          *
ACTTTCTTCA CCAAGTGCAA TAGATTACTG ATGTGATATT CTGTTGCTTT ACAGTTACAG
TGAAAGAAGT GGTTCACGTT ATCTAATGAC TACACTATAA GACAACGAAA TGTCAATGTC

1745 1750  1755 1760  1765 1770  1775 1780  1785 1790  1795 1800
        *          *          *          *          *          *
TTGATGTTTG GGGATCGATG TGCTCAGCCA AATTTCCTGT TTGAAATATC ATGTTAAATT
AACTACAAAC CCCTAGCTAC ACGAGTCGGT TTAAAGGACA AACTTTATAG TACAATTTAA

1805 1810  1815 1820  1825 1830  1835 1840  1845 1850  1855 1860
        *          *          *          *          *          *
AGAATGAATT TATCTTTACC AAAAACCATG TTGCGTTCAA AGAGGTGAAC ATTAAAATAT
TCTTACTTAA ATAGAAATGG TTTTTGGTAC AACGCAAGTT TCTCCACTTG TAATTTTATA

1865 1870  1875 1880  1885 1890  1895 1900  1905 1910  1915 1920
        *          *          *          *          *          *
AGAGACAGGA CAGAATGTGT TCTTTTCTCC TCTACCAGTC CTATTTTTCA ATGGGAAGAC
TCTCTGTCCT GTCTTACACA AGAAAAGAGG AGATGGTCAG GATAAAAAGT TACCCTTCTG

1925 1930  1935 1940  1945 1950  1955 1960  1965 1970  1975 1980
        *          *          *          *          *          *
TCAGGAGTCT GCCACTTGTC AAAGAAGGTG CTGATCCTAA GAATTTTTCA TTCTCAGAAT
AGTCCTCAGA CGGTGAACAG TTTCTTCCAC GACTAGGATT CTTAAAAAGT AAGAGTCTTA

1985 1990  1995 2000  2005 2010  2015 2020  2025 2030  2035 2040
        *          *          *          *          *          *
TCGGTGTGCT GCCAACTTGA TGTTCCACCT GCCACAAACC ACCAGGACTG AAAGAAGAAA
AGCCACACGA CGGTTGAACT ACAAGGTGGA CGGTGTTTGG TGGTCCTGAC TTTCTTCTTT

2045 2050  2055 2060  2065 2070  2075 2080  2085 2090  2095 2100
        *          *          *          *          *          *
ACAGTACAGA AGGCAAAGTT TACAGATGTT TTTAATTCTA GTATTTTATC TGGAACAACT
TGTCATGTCT TCCGTTTCAA ATGTCTACAA AAATTAAGAT CATAAAATAG ACCTTGTTGA

2105 2110  2115 2120  2125 2130  2135 2140  2145 2150  2155 2160
        *          *          *          *          *          *
TGTAGCAGCT ATATATTTCC CCTTGGTCCC AAGCCTGATA CTTTAGCCAT CATAACTCAC
ACATCGTCGA TATATAAAGG GGAACCAGGG TTCGGACTAT GAAATCGGTA GTATTGAGTG

2165 2170  2175 2180  2185 2190  2195 2200  2205 2210  2215 2220
        *          *          *          *          *          *
TAACAGGGAG AAGTAGCTAG TAGCAATGTG CCTTGATTGA TTAGATAAAG ATTTCTAGTA
ATTGTCCCTC TTCATCGATC ATCGTTACAC GGAACTAACT AATCTATTTC TAAAGATCAT

2225 2230  2235 2240  2245 2250  2255 2260  2265 2270  2275 2280
        *          *          *          *          *          *
GGCAGCAAAA GACCAAATCT CAGTTGTTTG CTTCTTGCCA TCACTGGTCC AGGTCTTCAG
CCGTCGTTTT CTGGTTTAGA GTCAACAAAC GAAGAACGGT AGTGACCAGG TCCAGAAGTC

2285 2290  2295 2300  2305 2310  2315 2320  2325 2330  2335 2340
        *          *          *          *          *          *
TTTCCGAATC TCTTTCCCTT CCCCTGTGGT CTATTGTCGC TATGTGACTT GCGCTTAATC
AAAGGCTTAG AGAAAGGGAA GGGGACACCA GATAACAGCG ATACACTGAA CGCGAATTAG

2345 2350  2355 2360  2365 2370  2375 2380  2385 2390  2395 2400
```

FIG. 7D

CAATATTTTG CCTTTTTTCT ATATCAAAAA ACCTTTACAG TTAGCAGGGA TGTTCCTTAC
GTTATAAAAC GGAAAAAAGA TATAGTTTTT TGGAAATGTC AATCGTCCCT ACAAGGAATG

2405 2410 2415 2420 2425 2430 2435 2440 2445 2450 2455 2460

CGAGGATTTT TAACCCCCAA TCTCTCATAA TCGCTAGTGT TTAAAAGGCT AAGAATAGTG
GCTCCTAAAA ATTGGGGGTT AGAGAGTATT AGCGATCACA AATTTTCCGA TTCTTATCAC

2465 2470 2475 2480 2485 2490 2495 2500 2505 2510 2515 2520

GGGCCCAACC GATGTGGTAG GTGATAAAGA GGCATCTTTT CTAGAGACAC ATTGGACCAG
CCCGGGTTGG CTACACCATC CACTATTTCT CCGTAGAAAA GATCTCTGTG TAACCTGGTC

2525 2530 2535 2540 2545 2550 2555 2560 2565 2570 2575 2580

ATGAGGATCC GAAACGGCAG CCTTTACGTT CATCACCTGC TAGAACCTCT CGTAGTCCAT
TACTCCTAGG CTTTGCCGTC GGAAATGCAA GTAGTGGACG ATCTTGGAGA GCATCAGGTA

2585 2590 2595 2600 2605 2610 2615 2620 2625 2630 2635 2640

CACCATTTCT TGGCATTGGA ATTCTACTGG AAAAAAATAC AAAAAGCAAA ACAAAACCCT
GTGGTAAAGA ACCGTAACCT TAAGATGACC TTTTTTTATG TTTTTCGTTT TGTTTTGGGA

2645 2650 2655 2660 2665 2670 2675 2680 2685 2690 2695 2700

CAGCACTGTT ACAAGAGGCC ATTTAAGTAT CTTGTGCTTC TTCACTTACC CATTAGCCAG
GTCGTGACAA TGTTCTCCGG TAAATTCATA GAACACGAAG AAGTGAATGG GTAATCGGTC

2705 2710 2715 2720 2725 2730 2735 2740 2745 2750 2755 2760

GTTCTCATTA GGTTTTGCTT GGGCCTCCCT GGCACTGAAC CTTAGGCTTT GTATGACAGT
CAAGAGTAAT CCAAAACGAA CCCGGAGGGA CCGTGACTTG GAATCCGAAA CATACTGTCA

2765 2770 2775 2780 2785 2790 2795 2800 2805 2810 2815 2820

GAAGCAGCAC TGTGAGTGGT TCAAGCACAC TGGAATATAA AACAGTCATG GCCTGAGATG
CTTCGTCGTG ACACTCACCA AGTTCGTGTG ACCTTATATT TTGTCAGTAC CGGACTCTAC

2825 2830 2835 2840 2845 2850 2855 2860 2865 2870 2875 2880

CAGGTGATGC CATTACAGAA CCAAATCGTG GCACGTATTG CTGTGTCTCC TCTCAGAGTG
GTCCACTACG GTAATGTCTT GGTTTAGCAC CGTGCATAAC GACACAGAGG AGAGTCTCAC

2885 2890 2895 2900 2905 2910 2915 2920 2925 2930 2935 2940

ACAGTCATAA ATACTGTCAA ACAATAAAGG GAGAATGGTG CTGTTTAAAG TCACATCCCT
TGTCAGTATT TATGACAGTT TGTTATTTCC CTCTTACCAC GACAAATTTC AGTGTAGGGA

2945 2950 2955 2960 2965 2970 2975 2980 2985 2990 2995 3000

GTAAATTGCA GAATTCAAAA GTGATTATCT CTTTGATCTA CTTGCCTCAT TTCCCTATCT
CATTTAACGT CTTAAGTTTT CACTAATAGA GAAACTAGAT GAACGGAGTA AAGGGATAGA

3005 3010 3015 3020 3025 3030 3035 3040 3045 3050 3055 3060

TCTCCCCCAC GGTATCCTAA ACTTTAGACT TCCCACTGTT CTGAAAGGAG ACATTGCTCT
AGAGGGGGTG CCATAGGATT TGAAATCTGA AGGGTGACAA GACTTTCCTC TGTAACGAGA

3065 3070 3075 3080 3085 3090 3095 3100 3105 3110 3115 3120

ATGTCTGCCT TCGACCACAG CAAGCCATCA TCCTCCATTG CTCCCGGGGA CTCAAGAGGA

FIG. 7E

```
TACAGACGGA AGCTGGTGTC GTTCGGTAGT AGGAGGTAAC GAGGGCCCCT GAGTTCTCCT

 3125 3130  3135 3140  3145 3150  3155 3160  3165 3170  3175 3180
         *          *          *          *          *          *
ATCTGTTTCT CTGCTGTCAA CTTCCCATCT GGCTCAGCAT AGGGTCACTT TGCCATTATG
TAGACAAAGA GACGACAGTT GAAGGGTAGA CCGAGTCGTA TCCCAGTGAA ACGGTAATAC

 3185 3190  3195 3200  3205 3210  3215 3220  3225 3230  3235 3240
         *          *          *          *          *          *
CAAATGGAGA TAAAAGCAAT TCTGGCTGTC CAGGAGCTAA TCTGACCGTT CTATTGTGTG
GTTTACCTCT ATTTTCGTTA AGACCGACAG GTCCTCGATT AGACTGGCAA GATAACACAC

 3245 3250  3255 3260  3265 3270  3275 3280  3285 3290  3295 3300
         *          *          *          *          *          *
GATGACCACA TAAGAAGGCA ATTTTAGTGT ATTAATCATA GATTATTATA AACTATAAAC
CTACTGGTGT ATTCTTCCGT TAAAATCACA TAATTAGTAT CTAATAATAT TTGATATTTG

 3305 3310  3315 3320  3325 3330  3335 3340  3345 3350  3355 3360
         *          *          *          *          *          *
TTAAGGGCAA GGAGTTTATT ACAATGTATC TTTATTAAAA CAAAAGGGTG TATAGTGTTC
AATTCCCGTT CCTCAAATAA TGTTACATAG AAATAATTTT GTTTTCCCAC ATATCACAAG

 3365 3370  3375 3380  3385 3390  3395 3400  3405 3410  3415 3420
         *          *          *          *          *          *
ACAAACTGTG AAAATAGTGT AAGAACTGTA CATTGTGAGC TCTGGTTATT TTTCTCTTGT
TGTTTGACAC TTTTATCACA TTCTTGACAT GTAACACTCG AGACCAATAA AAAGAGAACA

 3425 3430  3435 3440  3445 3450  3455 3460  3465 3470  3475 3480
         *          *          *          *          *          *
ACCATAGAAA AATGTATAAA AATTATCAAA AAGCTAATGT GCAGGGATAT TGCCTTATTT
TGGTATCTTT TTACATATTT TTAATAGTTT TTCGATTACA CGTCCCTATA ACGGAATAAA

 3485 3490  3495 3500  3505 3510  3515 3520  3525 3530  3535 3540
         *          *          *          *          *          *
GTCTGTAAAA AATGGAGCTC AGTAACATAA CTGCTTCTTG GAGCTTTGGA ATATTTTATC
CAGACATTTT TTACCTCGAG TCATTGTATT GACGAAGAAC CTCGAAACCT TATAAAATAG

 3545 3550
         *
CTGTATTCTT GTTT  (SEQ ID NO:7)
GACATAAGAA CAAA
```

FIG. 7F

```
         5        10        15        20        25        30        35        40        45        50
                   *                   *                   *                   *                   *
CTCCCAACA ATG GCG GCT CCG AGC CCG AGC GGC GGC GGC GGC TCC GGG GGC
GAGGGTTGT TAC CGC CGA GGC TCG GGC TCG CCG CCG CCG CCG AGG CCC CCG
          Met Ala Ala Pro Ser Pro Ser Gly Gly Gly Gly Ser Gly Gly>

    55        60        65        70        75        80        85        90        95
               *                   *                   *                   *
GGC AGC GGC AGC GGC ACC CCC GGC CCC GTA GGG TCC CCG GCG CCA GGC
CCG TCG CCG TCG CCG TGG GGG CCG GGG CAT CCC AGG GGC CGC GGT CCG
Gly Ser Gly Ser Gly Thr Pro Gly Pro Val Gly Ser Pro Ala Pro Gly>

100       105       110       115       120       125       130       135       140       145
 *                   *                   *                   *                   *
CAC CCG GCC GTC AGC AGC ATG CAG GGT AAA CGC AAA GCA CTG AAG TTG
GTG GGC CGG CAG TCG TCG TAC GTC CCA TTT GCG TTT CGT GAC TTC AAC
His Pro Ala Val Ser Ser Met Gln Gly Lys Arg Lys Ala Leu Lys Leu>

150       155       160       165       170       175       180       185       190       195
 *                   *                   *                   *                   *
AAT TTT GCA AAT CCA CCT TTC AAA TCT ACA GCA AGG TTT ACT CTG AAT
TTA AAA CGT TTA GGT GGA AAG TTT AGA TGT CGT TCC AAA TGA GAC TTA
Asn Phe Ala Asn Pro Pro Phe Lys Ser Thr Ala Arg Phe Thr Leu Asn>

    200       205       210       215       220       225       230       235       240
     *                   *                   *                   *                   *
CCC AAT CCT ACA GGA GTT CAA AAC CCA CAC ATA GAG AGA CTG AGA ACA
GGG TTA GGA TGT CCT CAA GTT TTG GGT GTG TAT CTC TCT GAC TCT TGT
Pro Asn Pro Thr Gly Val Gln Asn Pro His Ile Glu Arg Leu Arg Thr>

245       250       255       260       265       270       275       280       285       290
           *                   *                   *                   *                   *
CAC AGC ATT GAG TCA TCA GGA AAA CTG AAG ATC TCC CCT GAA CAA CAC
GTG TCG TAA CTC AGT AGT CCT TTT GAC TTC TAG AGG GGA CTT GTT GTG
His Ser Ile Glu Ser Ser Gly Lys Leu Lys Ile Ser Pro Glu Gln His>

    295       300       305       310       315       320       325       330       335
               *                   *                   *                   *
TGG GAT TTC ACT GCA GAG GAC TTG AAA GAC CTT GGA GAA ATT GGA CGA
ACC CTA AAG TGA CGT CTC CTG AAC TTT CTG GAA CCT CTT TAA CCT GCT
Trp Asp Phe Thr Ala Glu Asp Leu Lys Asp Leu Gly Glu Ile Gly Arg>

340       345       350       355       360       365       370       375       380       385
 *                   *                   *                   *                   *
GGA GCT TAT GGT TCT GTC AAC AAA ATG GTC CAC AAA CCA AGT GGG CAA
CCT CGA ATA CCA AGA CAG TTG TTT TAC CAG GTG TTT GGT TCA CCC GTT
Gly Ala Tyr Gly Ser Val Asn Lys Met Val His Lys Pro Ser Gly Gln>

390       395       400       405       410       415       420       425       430       435
 *                   *                   *                   *                   *
ATA ATG GCA GTT AAA AGA ATT CGG TCA ACA GTG GAT GAA AAA GAA CAA
TAT TAC CGT CAA TTT TCT TAA GCC AGT TGT CAC CTA CTT TTT CTT GTT
Ile Met Ala Val Lys Arg Ile Arg Ser Thr Val Asp Glu Lys Glu Gln>

    440       445       450       455       460       465       470       475       480
     *                   *                   *                   *                   *
AAA CAA CTT CTT ATG GAT TTG GAT GTA GTA ATG CGG AGT AGT GAT TGC
TTT GTT GAA GAA TAC CTA AAC CTA CAT CAT TAC GCC TCA TCA CTA ACG
Lys Gln Leu Leu Met Asp Leu Asp Val Val Met Arg Ser Ser Asp Cys>
```

FIG. 8A

```
485       490       495       500       505       510       515       520       525       530
CCA TAC ATT GTT CAG TTT TAT GGT GCA CTC TTC AGA GAG GGT GAC TGT
GGT ATG TAA CAA GTC AAA ATA CCA CGT GAG AAG TCT CTC CCA CTG ACA
Pro Tyr Ile Val Gln Phe Tyr Gly Ala Leu Phe Arg Glu Gly Asp Cys>

   535       540       545       550       555       560       565       570       575
TGG ATC TGT ATG GAA CTC ATG TCT ACC TCG TTT GAT AAG TTT TAC AAA
ACC TAG ACA TAC CTT GAG TAC AGA TGG AGC AAA CTA TTC AAA ATG TTT
Trp Ile Cys Met Glu Leu Met Ser Thr Ser Phe Asp Lys Phe Tyr Lys>

580       585       590       595       600       605       610       615       620       625
TAT GTA TAT AGT GTA TTA GAT GAT GTT ATT CCA GAA GAA ATT TTA GGC
ATA CAT ATA TCA CAT AAT CTA CTA CAA TAA GGT CTT CTT TAA AAT CCG
Tyr Val Tyr Ser Val Leu Asp Asp Val Ile Pro Glu Glu Ile Leu Gly>

630       635       640       645       650       655       660       665       670       675
AAA ATC ACT TTA GCA ACT GTG AAA GCA CTA AAC CAC TTA AAA GAA AAC
TTT TAG TGA AAT CGT TGA CAC TTT CGT GAT TTG GTG AAT TTT CTT TTG
Lys Ile Thr Leu Ala Thr Val Lys Ala Leu Asn His Leu Lys Glu Asn>

   680       685       690       695       700       705       710       715       720
TTG AAA ATT ATT CAC AGA GAT ATC AAA CCT TCC AAT ATT CTT CTG GAC
AAC TTT TAA TAA GTG TCT CTA TAG TTT GGA AGG TTA TAA GAA GAC CTG
Leu Lys Ile Ile His Arg Asp Ile Lys Pro Ser Asn Ile Leu Leu Asp>

725       730       735       740       745       750       755       760       765       770
AGA AGT GGA AAT ATT AAG CTC TGT GAC TTC GGC ATC AGT GGA CAG CTT
TCT TCA CCT TTA TAA TTC GAG ACA CTG AAG CCG TAG TCA CCT GTC GAA
Arg Ser Gly Asn Ile Lys Leu Cys Asp Phe Gly Ile Ser Gly Gln Leu>

   775       780       785       790       795       800       805       810       815
GTG GAC TCT ATT GCC AAG ACA AGA GAT GCT GGC TGT AGG CCA TAC ATG
CAC CTG AGA TAA CGG TTC TGT TCT CTA CGA CCG ACA TCC GGT ATG TAC
Val Asp Ser Ile Ala Lys Thr Arg Asp Ala Gly Cys Arg Pro Tyr Met>

820       825       830       835       840       845       850       855       860       865
GCA CCT GAA AGA ATA GAC CCA AGC GCA TCA CGA CAA GGA TAT GAT GTC
CGT GGA CTT TCT TAT CTG GGT TCG CGT AGT GCT GTT CCT ATA CTA CAG
Ala Pro Glu Arg Ile Asp Pro Ser Ala Ser Arg Gln Gly Tyr Asp Val>

870       875       880       885       890       895       900       905       910       915
CGC TCT GAT GTC TGG AGT TTG GGG ATC ACA TTG TAT GAG TTG GCC ACA
GCG AGA CTA CAG ACC TCA AAC CCC TAG TGT AAC ATA CTC AAC CGG TGT
Arg Ser Asp Val Trp Ser Leu Gly Ile Thr Leu Tyr Glu Leu Ala Thr>

   920       925       930       935       940       945       950       955       960
GGC CGA TTT CCT TAT CCA AAG TGG AAT AGT GTA TTT GAT CAA CTA ACA
CCG GCT AAA GGA ATA GGT TTC ACC TTA TCA CAT AAA CTA GTT GAT TGT
Gly Arg Phe Pro Tyr Pro Lys Trp Asn Ser Val Phe Asp Gln Leu Thr>

965       970       975       980       985       990       995       1000      1005      1010
```

FIG. 8B

```
CAA GTC GTG AAA GGA GAT CCT CCG CAG CTG AGT AAT TCT GAG GAA AGG
GTT CAG CAC TTT CCT CTA GGA GGC GTC GAC TCA TTA AGA CTC CTT TCC
Gln Val Val Lys Gly Asp Pro Pro Gln Leu Ser Asn Ser Glu Glu Arg>

  1015  1020    1025    1030  1035    1040    1045  1050    1055
           *               *             *               *
GAA TTC TCC CCG AGT TTC ATC AAC TTT GTC AAC TTG TGC CTT ACG AAG
CTT AAG AGG GGC TCA AAG TAG TTG AAA CAG TTG AAC ACG GAA TGC TTC
Glu Phe Ser Pro Ser Phe Ile Asn Phe Val Asn Leu Cys Leu Thr Lys>

1060  1065    1070    1075  1080    1085    1090  1095    1100    1105
 *               *             *               *             *
GAT GAA TCC AAA AGG CCA AAG TAT AAA GAG CTT CTG AAA CAT CCC TTT
CTA CTT AGG TTT TCC GGT TTC ATA TTT CTC GAA GAC TTT GTA GGG AAA
Asp Glu Ser Lys Arg Pro Lys Tyr Lys Glu Leu Leu Lys His Pro Phe>

  1110    1115    1120  1125    1130    1135  1140    1145    1150  1155
    *               *             *               *             *
ATT TTG ATG TAT GAA GAA CGT GCC GTT GAG GTC GCA TGC TAT GTT TGT
TAA AAC TAC ATA CTT CTT GCA CGG CAA CTC CAG CGT ACG ATA CAA ACA
Ile Leu Met Tyr Glu Glu Arg Ala Val Glu Val Ala Cys Tyr Val Cys>

    1160    1165  1170    1175    1180  1185    1190    1195  1200
      *               *             *               *             *
AAA ATC CTG GAT CAA ATG CCA GCT ACT CCC AGC TCT CCC ATG TAT GTC
TTT TAG GAC CTA GTT TAC GGT CGA TGA GGG TCG AGA GGG TAC ATA CAG
Lys Ile Leu Asp Gln Met Pro Ala Thr Pro Ser Ser Pro Met Tyr Val>

1205  1210  1215 1220  1225 1230  1235 1240  1245 1250  1255 1260
        *          *          *          *          *          *
GAT TGAT ATCGCTGCTA CATCAGACTC TAGAAAAAAG GGCTGAGAGG AAGCAAGACG
CTA ACTA TAGCGACGAT GTAGTCTGAG ATCTTTTTTC CCGACTCTCC TTCGTTCTGC
Asp>  (SEQ ID NO:10)

  1265 1270  1275 1280  1285 1290  1295 1300  1305 1310  1315 1320
          *          *          *          *          *          *
TAAAGAATTT TCATCCCGTA TCACAGTGTT TTTATTGCTC GCCCAGACAC CATGTGCAAT
ATTTCTTAAA AGTAGGGCAT AGTGTCACAA AAATAACGAG CGGGTCTGTG GTACACGTTA

  1325 1330  1335 1340  1345 1350  1355 1360  1365 1370  1375 1380
          *          *          *          *          *          *
AAGATTGGTG TTCGTTTCCA TCATGTCTGT ATACTCCTGT CACCTAGAAC GTGCATCCTT
TTCTAACCAC AAGCAAAGGT AGTACAGACA TATGAGGACA GTGGATCTTG CACGTAGGAA

  1385 1390  1395 1400  1405 1410  1415 1420  1425 1430  1435 1440
          *          *          *          *          *          *
GTAATACCTG ATTGATCACA CAGTGTTAGT GCTGGTCAGA GAGACCTCAT CCTGCTCTTT
CATTATGGAC TAACTAGTGT GTCACAATCA CGACCAGTCT CTCTGGAGTA GGACGAGAAA

  1445 1450  1455 1460  1465 1470  1475 1480  1485 1490  1495 1500
          *          *          *          *          *          *
TGTGATGAAC ATATTCATGA AATGTGGAAG TCAGTACGAT CAAGTTGTTG ACTGTGATTA
ACACTACTTG TATAAGTACT TTACACCTTC AGTCATGCTA GTTCAACAAC TGACACTAAT

  1505 1510  1515 1520  1525 1530  1535 1540  1545 1550  1555 1560
          *          *          *          *          *          *
GATCACATCT TAAATTCATT TCTAGACTCA AAACCTGGAG ATGCAGCTAC TGGAATGGTG
CTAGTGTAGA ATTTAAGTAA AGATCTGAGT TTTGGACCTC TACGTCGATG ACCTTACCAC

  1565 1570  1575 1580  1585 1590  1595 1600  1605 1610  1615 1620
          *          *          *          *          *          *
TTTTGTCAGA CTTCCAAATC CTGGAAGGAC ACAGTGATGA ATGTACTATA TCTGAACATA
```

FIG. 8C

```
AAAACAGTCT GAAGGTTTAG GACCTTCCTG TGTCACTACT TACATGATAT AGACTTGTAT

 1625 1630  1635 1640  1645 1650  1655 1660  1665 1670  1675 1680
         *          *          *          *          *          *
GAAACTCGGG CTTGAGTGAG AAGAGCTTGC ACAGCCAACG AGACACATTG CCTTCTGGAG
CTTTGAGCCC GAACTCACTC TTCTCGAACG TGTCGGTTGC TCTGTGTAAC GGAAGACCTC

 1685 1690  1695 1700  1705 1710  1715 1720  1725 1730  1735 1740
         *          *          *          *          *          *
CTGGGAGACA AAGGAGGAAT TTACTTTCTT CACCAAGTGC AATAGATTAC TGATGTGATA
GACCCTCTGT TTCCTCCTTA AATGAAAGAA GTGGTTCACG TTATCTAATG ACTACACTAT

 1745 1750  1755 1760  1765 1770  1775 1780  1785 1790  1795 1800
         *          *          *          *          *          *
TTCTGTTGCT TTACAGTTAC AGTTGATGTT TGGGGATCGA TGTGCTCAGC CAAATTTCCT
AAGACAACGA AATGTCAATG TCAACTACAA ACCCCTAGCT ACACGAGTCG GTTTAAAGGA

 1805 1810  1815 1820  1825 1830  1835 1840  1845 1850  1855 1860
         *          *          *          *          *          *
GTTTGAAATA TCATGTTAAA TTAGAATGAA TTTATCTTTA CCAAAAACCA TGTTGCGTTC
CAAACTTTAT AGTACAATTT AATCTTACTT AAATAGAAAT GGTTTTTGGT ACAACGCAAG

 1865 1870  1875 1880  1885 1890  1895 1900  1905 1910  1915 1920
         *          *          *          *          *          *
AAAGAGGTGA ACATTAAAAT ATAGAGACAG GACAGAATGT GTTCTTTTCT CCTCTACCAG
TTTCTCCACT TGTAATTTTA TATCTCTGTC CTGTCTTACA CAAGAAAAGA GGAGATGGTC

 1925 1930  1935 1940  1945 1950  1955 1960  1965 1970  1975 1980
         *          *          *          *          *          *
TCCTATTTTT CAATGGGAAG ACTCAGGAGT CTGCCACTTG TCAAAGAAGG TGCTGATCCT
AGGATAAAAA GTTACCCTTC TGAGTCCTCA GACGGTGAAC AGTTTCTTCC ACGACTAGGA

 1985 1990  1995 2000  2005 2010  2015 2020  2025 2030  2035 2040
         *          *          *          *          *          *
AAGAATTTTT CATTCTCAGA ATTCGGTGTG CTGCCAACTT GATGTTCCAC CTGCCACAAA
TTCTTAAAAA GTAAGAGTCT TAAGCCACAC GACGGTTGAA CTACAAGGTG GACGGTGTTT

 2045 2050  2055 2060  2065 2070  2075 2080  2085 2090  2095 2100
         *          *          *          *          *          *
CCACCAGGAC TGAAAGAAGA AAACAGTACA GAAGGCAAAG TTTACAGATG TTTTTAATTC
GGTGGTCCTG ACTTTCTTCT TTTGTCATGT CTTCCGTTTC AAATGTCTAC AAAAATTAAG

 2105 2110  2115 2120  2125 2130  2135 2140  2145 2150  2155 2160
         *          *          *          *          *          *
TAGTATTTTA TCTGGAACAA CTTGTAGCAG CTATATATTT CCCCTTGGTC CCAAGCCTGA
ATCATAAAAT AGACCTTGTT GAACATCGTC GATATATAAA GGGGAACCAG GGTTCGGACT

 2165 2170  2175 2180  2185 2190  2195 2200  2205 2210  2215 2220
         *          *          *          *          *          *
TACTTTAGCC ATCATAACTC ACTAACAGGG AGAAGTAGCT AGTAGCAATG TGCCTTGATT
ATGAAATCGG TAGTATTGAG TGATTGTCCC TCTTCATCGA TCATCGTTAC ACGGAACTAA

 2225 2230  2235 2240  2245 2250  2255 2260  2265 2270  2275 2280
         *          *          *          *          *          *
GATTAGATAA AGATTTCTAG TAGGCAGCAA AAGACCAAAT CTCAGTTGTT TGCTTCTTGC
CTAATCTATT TCTAAAGATC ATCCGTCGTT TTCTGGTTTA GAGTCAACAA ACGAAGAACG

 2285 2290  2295 2300  2305 2310  2315 2320  2325 2330  2335 2340
         *          *          *          *          *          *
CATCACTGGT CCAGGTCTTC AGTTTCCGAA TCTCTTTCCC TTCCCCTGTG GTCTATTGTC
GTAGTGACCA GGTCCAGAAG TCAAAGGCTT AGAGAAAGGG AAGGGGACAC CAGATAACAG
```

FIG. 8D

```
2345 2350   2355 2360   2365 2370   2375 2380   2385 2390   2395 2400
        *           *           *           *           *           *
GCTATGTGAC TTGCGCTTAA TCCAATATTT TGCCTTTTTT CTATATCAAA AAACCTTTAC
CGATACACTG AACGCGAATT AGGTTATAAA ACGGAAAAAA GATATAGTTT TTTGGAAATG

2405 2410   2415 2420   2425 2430   2435 2440   2445 2450   2455 2460
        *           *           *           *           *           *
AGTTAGCAGG GATGTTCCTT ACCGAGGATT TTTAACCCCC AATCTCTCAT AATCGCTAGT
TCAATCGTCC CTACAAGGAA TGGCTCCTAA AAATTGGGGG TTAGAGAGTA TTAGCGATCA

2465 2470   2475 2480   2485 2490   2495 2500   2505 2510   2515 2520
        *           *           *           *           *           *
GTTTAAAAGG CTAAGAATAG TGGGGCCCAA CCGATGTGGT AGGTGATAAA GAGGCATCTT
CAAATTTTCC GATTCTTATC ACCCCGGGTT GGCTACACCA TCCACTATTT CTCCGTAGAA

2525 2530   2535 2540   2545 2550   2555 2560   2565 2570   2575 2580
        *           *           *           *           *           *
TTCTAGAGAC ACATTGGACC AGATGAGGAT CCGAAACGGC AGCCTTTACG TTCATCACCT
AAGATCTCTG TGTAACCTGG TCTACTCCTA GGCTTTGCCG TCGGAAATGC AAGTAGTGGA

2585 2590   2595 2600   2605 2610   2615 2620   2625 2630   2635 2640
        *           *           *           *           *           *
GCTAGAACCT CTCGTAGTCC ATCACCATTT CTTGGCATTG GAATTCTACT GGAAAAAAAT
CGATCTTGGA GAGCATCAGG TAGTGGTAAA GAACCGTAAC CTTAAGATGA CCTTTTTTTA

2645 2650   2655 2660   2665 2670   2675 2680   2685 2690   2695 2700
        *           *           *           *           *           *
ACAAAAAGCA AAACAAAACC CTCAGCACTG TTACAAGAGG CCATTTAAGT ATCTTGTGCT
TGTTTTTCGT TTTGTTTTGG GAGTCGTGAC AATGTTCTCC GGTAAATTCA TAGAACACGA

2705 2710   2715 2720   2725 2730   2735 2740   2745 2750   2755 2760
        *           *           *           *           *           *
TCTTCACTTA CCCATTAGCC AGGTTCTCAT TAGGTTTTGC TTGGGCCTCC CTGGCACTGA
AGAAGTGAAT GGGTAATCGG TCCAAGAGTA ATCCAAAACG AACCCGGAGG GACCGTGACT

2765 2770   2775 2780   2785 2790   2795 2800   2805 2810   2815 2820
        *           *           *           *           *           *
ACCTTAGGCT TTGTATGACA GTGAAGCAGC ACTGTGAGTG GTTCAAGCAC ACTGGAATAT
TGGAATCCGA AACATACTGT CACTTCGTCG TGACACTCAC CAAGTTCGTG TGACCTTATA

2825 2830   2835 2840   2845 2850   2855 2860   2865 2870   2875 2880
        *           *           *           *           *           *
AAAACAGTCA TGGCCTGAGA TGCAGGTGAT GCCATTACAG AACCAAATCG TGGCACGTAT
TTTTGTCAGT ACCGGACTCT ACGTCCACTA CGGTAATGTC TTGGTTTAGC ACCGTGCATA

2885 2890   2895 2900   2905 2910   2915 2920   2925 2930   2935 2940
        *           *           *           *           *           *
TGCTGTGTCT CCTCTCAGAG TGACAGTCAT AAATACTGTC AAACAATAAA GGGAGAATGG
ACGACACAGA GGAGAGTCTC ACTGTCAGTA TTTATGACAG TTTGTTATTT CCCTCTTACC

2945 2950   2955 2960   2965 2970   2975 2980   2985 2990   2995 3000
        *           *           *           *           *           *
TGCTGTTTAA AGTCACATCC CTGTAAATTG CAGAATTCAA AAGTGATTAT CTCTTTGATC
ACGACAAATT TCAGTGTAGG GACATTTAAC GTCTTAAGTT TTCACTAATA GAGAAACTAG

3005 3010   3015 3020   3025 3030   3035 3040   3045 3050   3055 3060
        *           *           *           *           *           *
TACTTGCCTC ATTTCCCTAT CTTCTCCCCC ACGGTATCCT AAACTTTAGA CTTCCCACTG
ATGAACGGAG TAAAGGGATA GAAGAGGGGG TGCCATAGGA TTTGAAATCT GAAGGGTGAC

3065 3070   3075 3080   3085 3090   3095 3100   3105 3110   3115 3120
        *           *           *           *           *           *
```

FIG. 8E

```
TTCTGAAAGG AGACATTGCT CTATGTCTGC CTTCGACCAC AGCAAGCCAT CATCCTCCAT
AAGACTTTCC TCTGTAACGA GATACAGACG GAAGCTGGTG TCGTTCGGTA GTAGGAGGTA

 3125 3130  3135 3140  3145 3150  3155 3160  3165 3170  3175 3180
       *          *          *          *          *          *
TGCTCCCGGG GACTCAAGAG GAATCTGTTT CTCTGCTGTC AACTTCCCAT CTGGCTCAGC
ACGAGGGCCC CTGAGTTCTC CTTAGACAAA GAGACGACAG TTGAAGGGTA GACCGAGTCG

 3185 3190  3195 3200  3205 3210  3215 3220  3225 3230  3235 3240
       *          *          *          *          *          *
ATAGGGTCAC TTTGCCATTA TGCAAATGGA GATAAAAGCA ATTCTGGCTG TCCAGGAGCT
TATCCCAGTG AAACGGTAAT ACGTTTACCT CTATTTTCGT TAAGACCGAC AGGTCCTCGA

 3245 3250  3255 3260  3265 3270  3275 3280  3285 3290  3295 3300
       *          *          *          *          *          *
AATCTGACCG TTCTATTGTG TGGATGACCA CATAAGAAGG CAATTTTAGT GTATTAATCA
TTAGACTGGC AAGATAACAC ACCTACTGGT GTATTCTTCC GTTAAAATCA CATAATTAGT

 3305 3310  3315 3320  3325 3330  3335 3340  3345 3350  3355 3360
       *          *          *          *          *          *
TAGATTATTA TAAACTATAA ACTTAAGGGC AAGGAGTTTA TTACAATGTA TCTTTATTAA
ATCTAATAAT ATTTGATATT TGAATTCCCG TTCCTCAAAT AATGTTACAT AGAAATAATT

 3365 3370  3375 3380  3385 3390  3395 3400  3405 3410  3415 3420
       *          *          *          *          *          *
AACAAAAGGG TGTATAGTGT TCACAAACTG TGAAAATAGT GTAAGAACTG TACATTGTGA
TTGTTTTCCC ACATATCACA AGTGTTTGAC ACTTTTATCA CATTCTTGAC ATGTAACACT

 3425 3430  3435 3440  3445 3450  3455 3460  3465 3470  3475 3480
       *          *          *          *          *          *
GCTCTGGTTA TTTTTCTCTT GTACCATAGA AAAATGTATA AAAATTATCA AAAAGCTAAT
CGAGACCAAT AAAAAGAGAA CATGGTATCT TTTTACATAT TTTTAATAGT TTTTCGATTA

 3485 3490  3495 3500  3505 3510  3515 3520  3525 3530  3535 3540
       *          *          *          *          *          *
GTGCAGGGAT ATTGCCTTAT TTGTCTGTAA AAAATGGAGC TCAGTAACAT AACTGCTTCT
CACGTCCCTA TAACGGAATA AACAGACATT TTTTACCTCG AGTCATTGTA TTGACGAAGA

 3545 3550  3555 3560  3565 3570  3575
       *          *          *
TGGAGCTTTG GAATATTTTA TCCTGTATTC TTGTTT   (SEQ ID NO:9)
ACCTCGAAAC CTTATAAAAT AGGACATAAG AACAAA
```

FIG. 8F

```
          1                                                                        70
MKK7                                                               MLGLPSTLFTPRSMES
HEP       <SASSSSSSASAFASAAPATGTFGGTYTPPTTRVSRATPTLPMLSSGPGGGLNRTRPVILP.PT.PHPPV
MKK1                                                           MPKKKP--TPIQ.NPA-PDGSAVNG
MKK2                                                         MLARRKPVLPA.TINP.IAEGP.PT.
MKK3                                                                MSKPPA-----PN.TPPRN
MKK4      MAAPSPSGGGGSGGGSGSGTPGPVGSPAPGHPAVSSMQGKRKALKLNFANPPFKSTARFTLNPN.TGVQN
MKK5      <IGQVLPEATTTAFEYEDEDGDRITVRSDEEMKAMLSYYYSTVMEQQVNGQLIEP.QIFPRACK.PGERN
MKK6                                          MSQSKGKKRNPGLKIPKEAFEQPQ-----TSSTPPRD
Consensus

          71                                                      I                140
MKK7      IEIDQKLQEIMKQT-GYLTIG-----GQRYQAEI-------------NDLENLGEMGSGTCGQVWKMRFR
HEP       S.T.M..KI..E..-.K.N.N-----.RQ.PTD.--------------...KH..DL.N..S.N.V..MHL
MKK1      TSSAETNL.ALQKKLEE.ELDE----Q..KRL.AFLTQKQKVGELKDD.F.KIS.L.A.NG.V.F.VSHK
MKK2      EGASEANLVDLQKKLEE.ELDE----Q.KKRL.AFLTQKAKVGELKDD.F.RIS.L.A.NG.V.T.VQH.
MKK3      ----------LDSR-TFI..G-----DRNFEV.A-------------D..VTIS.L.R.AY.V.E.V.HA
MKK4      PH.ERLRTHSIESS-.K.K.SP----E.HWDFTA-------------E..KD...I.R.AY.S.N..VHK
MKK5      .HGLKVNTRAGPSQHSSPAVSDSLPSNSLKKSSAELKKILANGQMNEQ.IRYRDTL.H.NG.T.Y.AYHV
MKK6      ----------LDSK-ACIS.G-----N.NFEVKA-------------D.L.PIM.L.R.AY.V.E...HV
Consensus                                                   D      G G  G V K

          141  II                   III             IV                 V            210
MKK7      KTGHIIAVKQMRRSGNKEENKRILMDLDVVLKSHDCPYIVQCFGTFITNTDVFIAMELM-GTCAEKLKK-
HEP       SSNT.........T..A..................K...K.L.C.VRDP..W.C....-SM.FD..L.-
MKK1      PS.LVM.R.LIHLEIKPAIRNQ.IRE.Q.-.HECNSP...GFY.A.YSDGEIS.C..H.D.GSLDQVL.K
MKK2      PS.L.M.R.LIHLEIKPAIRNQ.IRE.Q.-.HECNSP...GFY.A.YSDGEIS.C..H.D.GSLDQVL.E
MKK3      QS.T.M...RI.A.V.SQ.Q..LL....INMRTV..F.T.TFY.ALFREG..W.C....D-.SLD.FYRK
MKK4      PS.Q.M...RI.S.VDEK.Q.QLL......MRSS.......FY.ALFREG.CW.C....-S.SFD.FY.Y
MKK5      PS.K.L...VILLDITL.LQ.Q.MSE.EILI.-C.SS..IGFY.A.FVENRIS.CTEF.D.GSLDDIG.-
MKK6      PS.Q.M...RI.A.V.SQ.Q..LL....ISMRTV...FTVTFY.ALFREG..W.C....-D-.SLD.FY.Q
Consensus   I A K                  L                 G         I     M
```

FIG. 9A

```
          211                                      VI                            VII          *   * 280
MKK7      ---RMQGPIPERILGKMTVAIVKALYYLKEKHGVIHRDVKPSNILLDERGQIKLCDFGISGRLVDSKAKT
HEP       ---LSKK.V..Q....V...T.N..S...D..............I....N.................N.
MKK1      -----A.R...Q....VSI.VIKG.T..R...KIM.........VNS..E.......V..Q.I..M.NS
MKK2      -----AKR...E....VSI.VLRG.A..R...QIM.........VNS..E.......V..Q.I..M.NS
MKK3      VLDK-NMT...D...EIA.S..R..EH.HS.LS.I........V.INKE.HV.M.......Y....V...
MKK4      VYSVLDDV...E....I.L.T.K..NH...NLKII...I.......DRS.N..........Q....I...
MKK5      --------M..HV..RIA..V.KG.T..WS-LKIL........M.VNT...V......V.TQ..N.I...
MKK6      VIDK-GQT...D....IA.S.....EH.HS.LS.I........V.INAL..V.M.......Y....V...
Consensus         PE ILG         L   L        HRD KPSN L     G  K CDFG S  LV S A

          281     VIII                   IX                                      350
MKK7      RSAGCAAYMAPERIDPPDPTKPDYDIRADVWSLGISLVELATGQFPYKNCKTD-----------------
HEP       ...............---..K..K...........T......ARS..EG.N..----------------
MKK1      F-V.TRS..S...LQGTH-----.SVQS.I..M.L....M.V.RY.IPPPDAKELELMFGCQV----EGD
MKK2      F-V.TRS......LQGTH-----.SVQS.I..M.L......V.RY.IPPPDAKELEAIFGRPVVDGEEGE
MKK3      MD...KP.......N-.ELNQKG.NVKS.......TMI.M.ILR...ESWG.P-----------------
MKK4      .D...RP........-.SASRQG..V.S.......T.Y.....R...PKWNSV-----------------
MKK5      Y-V.TN........SGEQ-----.G.HS........FM.IQKN.GSLMP---------------------
MKK6      ID...KP.......N-.ELNQKG.SVKS.I.....TMI...ILR...DSWG.P-----------------
Consensus    G   YM PER             Y     D WSLG     E

          351                                X                                XI  420
MKK7      ----------------------------FEVLTKVLQEEPPLLP-G-HMGFSGDFQSFVKDCLTKDHRKR
HEP       ----------------------------........DS...C..Y.EGYN..QQ.RD..IK....N.QD.
MKK1      AAETPPRPRTPGRPLSSYGMDSRPPMAI..L.DYIVN.P..K..S.V---..LE..D..NK..I.NPAE.
MKK2      PHSISPRPRPPGRPVSGHGMDSRPAMAI..L.DYIVN.P..K..N.V---.TP...E..NK..I.NPAE.
MKK3      ----------------------------.QQ.KQ.VE.PS.Q..AD---R..PE.VD.TAQ..R.NPAE.
MKK4      ----------------------------.DQ..Q.VKGD..Q.SNSEERE..PS.IN..NL.....ES..
MKK5      ----------------------------LQL.QCIVD.DS.V..V.E---..EP.VH.ITQ.MR.QPKE.
MKK6      ----------------------------.QQ.KQ.V...S.Q..AD---K..AE.VD.TSQ..K.NSKE.
Consensus                                 L         P L        F       F    CL K    R

          421                                                  473
MKK7      PKYNKLLEHSFIKHYEILEVDVAS-WFKDVMAKTESPRTSGVLSQHHLPFFR  (SEQ ID NO: 18)
HEP       ...PE..AQP..RI..SAK...PN-..QSI--.DNRL.AN.DPTLQR..NS  (SEQ ID NO: 21)
MKK1      ADLKQ.MV.A...RSDAE...F.G-.LCSTIGLNQPSTPTHAAGV        (SEQ ID NO: 11)
MKK2      ADLKM.TN.T...RS.VE...F.G-.LCKTLRLNQPGTPTRTAV         (SEQ ID NO: 12)
MKK3      MS.LE.M..P.FTLHKTKKT.I.A-FV.KILGEDS                  (SEQ ID NO: 2)
MKK4      ...KE..K.P..LMY.ERA.E..C-YVCKILDQMPATP.SPMYVD        (SEQ ID NO: 10)
MKK5      .APEE.MG.P..VQFNDGNAA.VSM.VCRALEERRTSRGPREAAAGH      (SEQ ID NO: 22)
MKK6      .T.PE.MQ.P.FTLH.SKGT....-FVKLILGD                    (SEQ ID NO: 4)
Consensus       L     F                                        (SEQ ID NO: 27)
```

FIG. 9B

MKK7

32/54

Sequence Range: 1 to 1623

```
        10         20         30         40         50         60
GGAAAGGCAG CCTCCTGTAG GTGAAAATTC TGTTCACTAC CTGGCCACCT GGCCTGACTG
CCTTTCCGTC GGAGGACATC CACTTTTAAG ACAAGTGATG GACCGGTGGA CCGGACTGAC

        70         80         90        100        110        120
ACCTTCACAG CTTGATCATC TTCCTGAAGA GGCATTCAGG ATTCCCTCCA TCCCTACCCC
TGGAAGTGTC GAACTAGTAG AAGGACTTCT CCGTAAGTCC TAAGGGAGGT AGGGATGGGG

       130        140        150        160        170        180
TTCTGGACAA AGTCTTCCAC GTTTCCTTCC TGGGAGTTTC TTCCAGGAAC TGGAGATACC
AAGACCTGTT TCAGAAGGTG CAAAGGAAGG ACCCTCAAAG AAGGTCCTTG ACCTCTATGG

       190        200        210        220        230        240
CAGAGCCCTG CAACTCCCAC TGGCCAACGA TGGGGGCAGC CGCTCACCAT CCTCAGAGAG
GTCTCGGGAC GTTGAGGGTG ACCGGTTGCT ACCCCCGTCG GCGAGTGGTA GGAGTCTCTC

       250        260        270        280          290
CTCCCCACAG CACCCTACAC CCCCCACCCG GCCCCGCCAC ATG CTG GGG CTC CCA
GAGGGGTGTC GTGGGATGTG GGGGGTGGGC CGGGGCGGTG TAC GAC CCC GAG GGT
                                            Met Leu Gly Leu Pro>

    300         310          320         330         340
TCA ACC TTG TTC ACA CCG CGC AGT ATG GAG AGC ATC GAG ATT GAC CAG
AGT TGG AAC AAG TGT GGC GCG TCA TAC CTC TCG TAG CTC TAA CTG GTC
Ser Thr Leu Phe Thr Pro Arg Ser Met Glu Ser Ile Glu Ile Asp Gln>

      350         360         370          380         390
AAG CTG CAG GAG ATC ATG AAG CAG ACA GGG TAC CTG ACT ATC GGG GGC
TTC GAC GTC CTC TAG TAC TTC GTC TGT CCC ATG GAC TGA TAG CCC CCG
Lys Leu Gln Glu Ile Met Lys Gln Thr Gly Tyr Leu Thr Ile Gly Gly>

        400         410          420         430
CAG CGT TAT CAG GCA GAA ATC AAT GAC TTG GAG AAC TTG GGT GAG ATG
GTC GCA ATA GTC CGT CTT TAG TTA CTG AAC CTC TTG AAC CCA CTC TAC
Gln Arg Tyr Gln Ala Glu Ile Asn Asp Leu Glu Asn Leu Gly Glu Met>

440          450          460          470         480
GGC AGT GGT ACC TGT GGT CAG GTG TGG AAG ATG CGG TTC CGG AAG ACA
CCG TCA CCA TGG ACA CCA GTC CAC ACC TTC TAC GCC AAG GCC TTC TGT
Gly Ser Gly Thr Cys Gly Gln Val Trp Lys Met Arg Phe Arg Lys Thr>

490          500          510          520         530
GGC CAC ATC ATT GCT GTT AAG CAA ATG CGG CGC TCT GGG AAC AAG GAA
CCG GTG TAG TAA CGA CAA TTC GTT TAC GCC GCG AGA CCC TTG TTC CTT
Gly His Ile Ile Ala Val Lys Gln Met Arg Arg Ser Gly Asn Lys Glu
```

FIG. 10A

MKK7

```
  540         550         560         570         580
GAG AAT AAG CGC ATT TTG ATG GAC CTG GAT GTA GTA CTC AAG AGC CAT
CTC TTA TTC GCG TAA AAC TAC CTG GAC CTA CAT CAT GAG TTC TCG GTA
Glu Asn Lys Arg Ile Leu Met Asp Leu Asp Val Val Leu Lys Ser His>

      590         600         610         620         630
GAC TGC CCT TAC ATC GTT CAG TGC TTT GGC ACC TTC ATC ACC AAC ACA
CTG ACG GGA ATG TAG CAA GTC ACG AAA CCG TGG AAG TAG TGG TTG TGT
Asp Cys Pro Tyr Ile Val Gln Cys Phe Gly Thr Phe Ile Thr Asn Thr>

        640         650         660         670
GAC GTC TTT ATT GCC ATG GAG CTC ATG GGC ACA TGT GCA GAG AAG CTG
CTG CAG AAA TAA CGG TAC CTC GAG TAC CCG TGT ACA CGT CTC TTC GAC
Asp Val Phe Ile Ala Met Glu Leu Met Gly Thr Cys Ala Glu Lys Leu>

680         690         700         710         720
AAG AAA CGA ATG CAG GGC CCC ATT CCA GAG CGA ATC CTG GGC AAG ATG
TTC TTT GCT TAC GTC CCG GGG TAA GGT CTC GCT TAG GAC CCG TTC TAC
Lys Lys Arg Met Gln Gly Pro Ile Pro Glu Arg Ile Leu Gly Lys Met>

730         740         750         760         770
ACT GTG GCG ATT GTG AAA GCA CTG TAC TAT CTG AAG GAG AAG CAT GGC
TGA CAC CGC TAA CAC TTT CGT GAC ATG ATA GAC TTC CTC TTC GTA CCG
Thr Val Ala Ile Val Lys Ala Leu Tyr Tyr Leu Lys Glu Lys His Gly>

    780         790         800         810         820
GTC ATC CAT CGC GAT GTC AAA CCC TCC AAC ATC CTG CTA GAT GAG CGG
CAG TAG GTA GCG CTA CAG TTT GGG AGG TTG TAG GAC GAT CTA CTC GCC
Val Ile His Arg Asp Val Lys Pro Ser Asn Ile Leu Leu Asp Glu Arg>

      830         840         850         860         870
GGC CAG ATC AAG CTC TGT GAC TTT GGC ATC AGT GGC CGC CTT GTT GAC
CCG GTC TAG TTC GAG ACA CTG AAA CCG TAG TCA CCG GCG GAA CAA CTG
Gly Gln Ile Lys Leu Cys Asp Phe Gly Ile Ser Gly Arg Leu Val Asp>

        880         890         900         910
TCC AAA GCC AAA ACA CGG AGT GCT GGC TGT GCT GCC TAT ATG GCT CCC
AGG TTT CGG TTT TGT GCC TCA CGA CCG ACA CGA CGG ATA TAC CGA GGG
Ser Lys Ala Lys Thr Arg Ser Ala Gly Cys Ala Ala Tyr Met Ala Pro>

920         930         940         950         960
GAG CGC ATC GAC CCT CCA GAT CCC ACC AAG CCT GAC TAT GAC ATC CGA
CTC GCG TAG CTG GGA GGT CTA GGG TGG TTG GGA CTG ATA CTG TAG GCT
Glu Arg Ile Asp Pro Pro Asp Pro Thr Lys Pro Asp Tyr Asp Ile Arg>
```

FIG. 10B

MKK7

```
970            980            990            1000           1010
GCT GAT GTG TGG AGC CTG GGC ATC TCA CTG GTG GAG CTG GCA ACA GGA
CGA CTA CAC ACC TCG GAC CCG TAG AGT GAC CAC CTC GAC CGT TGT CCT
Ala Asp Val Trp Ser Leu Gly Ile Ser Leu Val Glu Leu Ala Thr Gly>

   1020           1030           1040           1050           1060
CAG TTC CCC TAT AAG AAC TGC AAG ACG GAC TTT GAG GTC CTC ACC AAA
GTC AAG GGG ATA TTC TTG ACG TTC TGC CTG AAA CTC CAG GAG TGG TTT
Gln Phe Pro Tyr Lys Asn Cys Lys Thr Asp Phe Glu Val Leu Thr Lys>

      1070           1080           1090           1100           1110
GTC CTA CAG GAA GAG CCC CCA CTC CTG CCT GGT CAC ATG GGC TTC TCA
CAG GAT GTC CTT CTC GGG GGT GAG GAC GGA CCA GTG TAC CCG AAG AGT
Val Leu Gln Glu Glu Pro Pro Leu Leu Pro Gly His Met Gly Phe Ser>

        1120           1130           1140           1150
GGG GAC TTC CAG TCA TTT GTC AAA GAC TGC CTT ACT AAA GAT CAC AGG
CCC CTG AAG GTC AGT AAA CAG TTT CTG ACG GAA TGA TTT CTA GTG TCC
Gly Asp Phe Gln Ser Phe Val Lys Asp Cys Leu Thr Lys Asp His Arg>

1160           1170           1180           1190           1200
AAG AGA CCA AAG TAT AAT AAG CTA CTT GAA CAC AGC TTC ATC AAG CAC
TTC TCT GGT TTC ATA TTA TTC GAT GAA CTT GTG TCG AAG TAG TTC GTG
Lys Arg Pro Lys Tyr Asn Lys Leu Leu Glu His Ser Phe Ile Lys His>

1210           1220           1230           1240           1250
TAT GAG ATA CTC GAG GTG GAT GTC GCG TCC TGG TTT AAG GAT GTC ATG
ATA CTC TAT GAG CTC CAC CTA CAG CGC AGG ACC AAA TTC CTA CAG TAC
Tyr Glu Ile Leu Glu Val Asp Val Ala Ser Trp Phe Lys Asp Val Met>

   1260           1270           1280           1290           1300
GCG AAG ACC GAG TCC CCA AGG ACT AGT GGA GTC CTG AGT CAG CAC CAT
CGC TTC TGG CTC AGG GGT TCC TGA TCA CCT CAG GAC TCA GTC GTG GTA
Ala Lys Thr Glu Ser Pro Arg Thr Ser Gly Val Leu Ser Gln His His>

      1310           1320           1330           1340           1350           1360
CTG CCC TTC TTC AGG TA GCCTCATGGC AGCGGCCAGC CCCGCAGGGG CCCCGGGCCA
GAC GGG AAG AAG TCC AT CGGAGTACCG TCGCCGGTCG GGGCGTCCCC GGGGCCCGGT
Leu Pro Phe Phe Arg>

      1370           1380           1390           1400           1410           1420
CGGCCACCGA CCCCCCCCCC AACCTGGCCA ACCCAGCTGC CCATCAGGGG ACCTGGGACC
GCCGGTGGCT GGGGGGGGGG TTGGACCGGT TGGGTCGACG GGTAGTCCCC TGGACCCTGG
```

FIG. 10C

MKK7

```
         1430       1440       1450       1460       1470       1480
    *    *     *    *     *    *     *    *     *    *     *    *
TGGACGACTG CCAAGGACTG AGGACAGAAA GTAGGGGGTT CCCATCCAGC TCTGACTCCC
ACCTGCTGAC GGTTCCTGAC TCCTGTCTTT CATCCCCCAA GGGTAGGTCG AGACTGAGGG

         1490       1500       1510       1520       1530       1540
    *    *     *    *     *    *     *    *     *    *     *    *
TGCCTACCAG CTGTGGACAA AAGGGCATGC TGGTTCCTAA TCCCTCCCAC TCTGGGGTCA
ACGGATGGTC GACACCTGTT TTCCCGTACG ACCAAGGATT AGGGAGGGTG AGACCCCAGT

         1550       1560       1570       1580       1590       1600
    *    *     *    *     *    *     *    *     *    *     *    *
GCCAGCAGTG TGAGCCCCAT CCCACCCCGA CAGACACTGT GAACGGAAGA CAGCAGGCCA
CGGTCGTCAC ACTCGGGGTA GGGTGGGGCT GTCTGTGACA CTTGCCTTCT GTCGTCCGGT

         1610       1620
    *    *     *    *
AAAAAAAAAA AAAAAAAAAA AAA  (SEQ ID NO: 17)
TTTTTTTTTT TTTTTTTTTT TTT
```

FIG. 10D

MKK7b 36/54
Sequence Range: 1 to 1465

```
                10           20            30           40           50
GC ACG AGC CCT GCT CCT GCC CCG TCC CAG CGA GCA GCC CTG CAA CTC CCA
CG TGC TCG GGA CGA GGA CGG GGC AGG GTC GCT CGT CGG GAC GTT GAG GGT
   Thr Ser Pro Ala Pro Ala Pro Ser Gln Arg Ala Ala Leu Gln Leu Pro>

               60           70           80           90
CTG GCC AAC GAT GGG GGC AGC CGC TCA CCA TCC TCA GAG AGC TCC CCA
GAC CGG TTG CTA CCC CCG TCG GCG AGT GGT AGG AGT CTC TCG AGG GGT
Leu Ala Asn Asp Gly Gly Ser Arg Ser Pro Ser Ser Glu Ser Ser Pro>

100            110          120          130          140
CAG CAC CCT ACA CCC CCC ACC CGG CCC CGC CAC ATG CTG GGG CTC CCA
GTC GTG GGA TGT GGG GGG TGG GCC GGG GCG GTG TAC GAC CCC GAG GGT
Gln His Pro Thr Pro Pro Thr Arg Pro Arg His Met Leu Gly Leu Pro>

   150          160          170          180          190
TCA ACC TTG TTC ACA CCG CGC AGT ATG GAG AGC ATC GAG ATT GAC CAG
AGT TGG AAC AAG TGT GGC GCG TCA TAC CTC TCG TAG CTC TAA CTG GTC
Ser Thr Leu Phe Thr Pro Arg Ser Met Glu Ser Ile Glu Ile Asp Gln>

    200          210          220          230          240
AAG CTG CAG GAG ATC ATG AAG CAG ACA GGG TAC CTG ACT ATC GGG GGC
TTC GAC GTC CTC TAG TAC TTC GTC TGT CCC ATG GAC TGA TAG CCC CCG
Lys Leu Gln Glu Ile Met Lys Gln Thr Gly Tyr Leu Thr Ile Gly Gly>

       250          260          270          280          290
CAG CGT TAT CAG GCA GAA ATC AAT GAC TTG GAG AAC TTG GGT GAG ATG
GTC GCA ATA GTC CGT CTT TAG TTA CTG AAC CTC TTG AAC CCA CTC TAC
Gln Arg Tyr Gln Ala Glu Ile Asn Asp Leu Glu Asn Leu Gly Glu Met>

           300          310          320          330
GGC AGT GGT ACC TGT GGT CAG GTG TGG AAG ATG CGG TTC CGG AAG ACA
CCG TCA CCA TGG ACA CCA GTC CAC ACC TTC TAC GCC AAG GCC TTC TGT
Gly Ser Gly Thr Cys Gly Gln Val Trp Lys Met Arg Phe Arg Lys Thr>

340            350          360          370          380
GGC CAC ATC ATT GCT GTT AAG CAA ATG CGG CGC TCT GGG AAC AAG GAA
CCG GTG TAG TAA CGA CAA TTC GTT TAC GCC GCG AGA CCC TTG TTC CTT
Gly His Ile Ile Ala Val Lys Gln Met Arg Arg Ser Gly Asn Lys Glu>

   390          400          410          420          430
GAG AAT AAG CGC ATT TTG ATG GAC CTG GAT GTA GTA CTC AAG AGC CAT
CTC TTA TTC GCG TAA AAC TAC CTG GAC CTA CAT CAT GAG TTC TCG GTA
Glu Asn Lys Arg Ile Leu Met Asp Leu Asp Val Val Leu Lys Ser His>
```

FIG. 11A

MKK7b

```
    440         450         460         470         480
GAC TGC CCT TAC ATC GTT CAG TGC TTT GGC ACC TTC ATC ACC AAC ACA
CTG ACG GGA ATG TAG CAA GTC ACG AAA CCG TGG AAG TAG TGG TTG TGT
Asp Cys Pro Tyr Ile Val Gln Cys Phe Gly Thr Phe Ile Thr Asn Thr>

        490         500         510         520         530
GAC GTC TTT ATT GCC ATG GAG CTC ATG GGC ACA TGT GCA GAG AAG CTG
CTG CAG AAA TAA CGG TAC CTC GAG TAC CCG TGT ACA CGT CTC TTC GAC
Asp Val Phe Ile Ala Met Glu Leu Met Gly Thr Cys Ala Glu Lys Leu>

            540         550         560         570
AAG AAA CGA ATG CAG GGC CCC ATT CCA GAG CGA ATC CTG GGC AAG ATG
TTC TTT GCT TAC GTC CCG GGG TAA GGT CTC GCT TAG GAC CCG TTC TAC
Lys Lys Arg Met Gln Gly Pro Ile Pro Glu Arg Ile Leu Gly Lys Met>

580         590         600         610         620
ACT GTG GCG ATT GTG AAA GCA CTG TAC TAT CTG AAG GAG AAG CAT GGC
TGA CAC CGC TAA CAC TTT CGT GAC ATG ATA GAC TTC CTC TTC GTA CCG
Thr Val Ala Ile Val Lys Ala Leu Tyr Tyr Leu Lys Glu Lys His Gly>

    630         640         650         660         670
GTC ATC CAT CGC GAT GTC AAA CCC TCC AAC ATC CTG CTA GAT GAG CGG
CAG TAG GTA GCG CTA CAG TTT GGG AGG TTG TAG GAC GAT CTA CTC GCC
Val Ile His Arg Asp Val Lys Pro Ser Asn Ile Leu Leu Asp Glu Arg>

        680         690         700         710         720
GGC CAG ATC AAG CTC TGT GAC TTT GGC ATC AGT GGC CGC CTT GTT GAC
CCG GTC TAG TTC GAG ACA CTG AAA CCG TAG TCA CCG GCG GAA CAA CTG
Gly Gln Ile Lys Leu Cys Asp Phe Gly Ile Ser Gly Arg Leu Val Asp>

        730         740         750         760         770
TCC AAA GCC AAA ACA CGG AGT GCT GGC TGT GCT GCC TAT ATG GCT CCC
AGG TTT CGG TTT TGT GCC TCA CGA CCG ACA CGA CGG ATA TAC CGA GGG
Ser Lys Ala Lys Thr Arg Ser Ala Gly Cys Ala Ala Tyr Met Ala Pro>

            780         790         800         810
GAG CGC ATC GAC CCT CCA GAT CCC ACC AAG CCT GAC TAT GAC ATC CGA
CTC GCG TAG CTG GGA GGT CTA GGG TGG TTC GGA CTG ATA CTG TAG GCT
Glu Arg Ile Asp Pro Pro Asp Pro Thr Lys Pro Asp Tyr Asp Ile Arg>
```

FIG. 11B

MKK7b


```
820       830        840        850        860
GCT GAT GTG TGG AGC CTG GGC ATC TCA CTG GTG GAG CTG GCA ACA GGA
CGA CTA CAC ACC TCG GAC CCG TAG AGT GAC CAC CTC GAC CGT TGT CCT
Ala Asp Val Trp Ser Leu Gly Ile Ser Leu Val Glu Leu Ala Thr Gly>

    870        880        890        900        910
CAG TTC CCC TAT AAG AAC TGC AAG ACG GAC TTT GAG GTC CTC ACC AAA
GTC AAG GGG ATA TTC TTG ACG TTC TGC CTG AAA CTC CAG GAG TGG TTT
Gln Phe Pro Tyr Lys Asn Cys Lys Thr Asp Phe Glu Val Leu Thr Lys>

      920        930        940        950        960
GTC CTA CAG GAA GAG CCC CCA CTC CTG CCT GGT CAC ATG GGC TTC TCA
CAG GAT GTC CTT CTC GGG GGT GAG GAC GGA CCA GTG TAC CCG AAG AGT
Val Leu Gln Glu Glu Pro Pro Leu Leu Pro Gly His Met Gly Phe Ser>

        970        980        990       1000       1010
GGG GAC TTC CAG TCA TTT GTC AAA GAC TGC CTT ACT AAA GAT CAC AGG
CCC CTG AAG GTC AGT AAA CAG TTT CTG ACG GAA TGA TTT CTA GTG TCC
Gly Asp Phe Gln Ser Phe Val Lys Asp Cys Leu Thr Lys Asp His Arg>

          1020       1030       1040       1050
AAG AGA CCA AAG TAT AAT AAG CTA CTT GAA CAC AGC TTC ATC AAG CAC
TTC TCT GGT TTC ATA TTA TTC GAT GAA CTT GTG TCG AAG TAG TTC GTG
Lys Arg Pro Lys Tyr Asn Lys Leu Leu Glu His Ser Phe Ile Lys His>

1060       1070       1080       1090       1100
TAT GAG ATA CTC GAG GTG GAT GTC GCG TCC TGG TTT AAG GAT GTC ATG
ATA CTC TAT GAG CTC CAC CTA CAG CGC AGG ACC AAA TTC CTA CAG TAC
Tyr Glu Ile Leu Glu Val Asp Val Ala Ser Trp Phe Lys Asp Val Met>

  1110       1120       1130       1140       1150
GCG AAG ACC GAG TCC CCA AGG ACT AGT GGA GTC CTG AGT CAG CAC CAT
CGC TTC TGG CTC AGG GGT TCC TGA TCA CCT CAG GAC TCA GTC GTG GTA
Ala Lys Thr Glu Ser Pro Arg Thr Ser Gly Val Leu Ser Gln His His>

    1160       1170       1180       1190       1200       1210
CTG CCC TTC TTC AGG T AGCCTCATGG CAGCGGCCAG CCCCGCAGGG GCCCCGGGCC
GAC GGG AAG AAG TCC A TCGGAGTACC GTCGCCGGTC GGGGCGTCCC CGGGGCCCGG
Leu Pro Phe Phe Arg> (SEQ ID NO: 20)

      1220       1230       1240       1250       1260       1270
ACGGCCACCG ACCCCCCCCC CAACCTGGCC AACCCAGCTG CCCATCAGGG GACCTGGGAC
TGCCGGTGGC TGGGGGGGGG GTTGGACCGG TTGGGTCGAC GGGTAGTCCC CTGGACCCTG

      1280       1290       1300       1310       1320       1330
CTGGACGACT GCCAAGGACT GAGGACAGAA AGTAGGGGGT TCCCATCCAG CTCTGACTCC
GACCTGCTGA CGGTTCCTGA CTCCTGTCTT TCATCCCCCA AGGGTAGGTC GAGACTGAGG
```

FIG. 11C

MKK7b

```
      1340       1350       1360       1370       1380       1390
    .    .     .    .     .    .     .    .     .    .     .    .
CTGCCTACCA GCTGTGGACA AAAGGGCATG CTGGTTCCTA ATCCCTCCCA CTCTGGGGTC
GACGGATGGT CGACACCTGT TTTCCCGTAC GACCAAGGAT TAGGGAGGGT GAGACCCCAG

      1400       1410       1420       1430       1440       1450
    .    .     .    .     .    .     .    .     .    .     .    .
AGCCAGCAGT GTGAGCCCCA TCCCACCCCG ACAGACACTG TGAACGGAAG ACAGCAAAAA
TCGGTCGTCA CACTCGGGGT AGGGTGGGGC TGTCTGTGAC ACTTGCCTTC TGTCGTTTTT

      1460
    .    .     .
AAAAAAAAAA AAAAA  (SEQ ID NO: 19)
TTTTTTTTTT TTTTT
```

FIG. 11D

Human MKK7
Sequence Range: 1 to 843

```
        10         20         30         40         50         60
TGTTTGTCTG CCGGACTGAC GGGCGGCCGG GCGGTGCGCG GCGGCGGTGG CGGCGGGGAA
ACAAACAGAC GGCCTGACTG CCCGCCGGCC CGCCACGCGC CGCCGCCACC GCCGCCCCTT

          70          80          90         100
G ATG GCG GCG TCC TCC CTG GAA CAG AAG CTG TCC CGC CTG GAA GCA AAG
C TAC CGC CGC AGG AGG GAC CTT GTC TTC GAC AGG GCG GAC CTT CGT TTC
  Met Ala Ala Ser Ser Leu Glu Gln Lys Leu Ser Arg Leu Glu Ala Lys>

110         120         130         140         150
CTG AAG CAG GAG AAC CGG GAG GCC CGG CGG AGG ATC GAC CTC AAC CTG
GAC TTC GTC CTC TTG GCC CTC CGG GCC GCC TCC TAG CTG GAG TTG GAC
Leu Lys Gln Glu Asn Arg Glu Ala Arg Arg Arg Ile Asp Leu Asn Leu>

160         170         180         190         200
GAT ATC AGC CCC CAG CGG CCC AGG CCC ACC CTG CAG CTC CCG CTG GCC
CTA TAG TCG GGG GTC GCC GGG TCC GGG TGG GAC GTC GAG GGC GAC CGG
Asp Ile Ser Pro Gln Arg Pro Arg Pro Thr Leu Gln Leu Pro Leu Ala>

   210         220         230         240         250
AAC GAT GGG GGC AGC CGC TCG CCA TCC TCA GAG AGC TCC CCG CAG CAC
TTG CTA CCC CCG TCG GCG AGC GGT AGG AGT CTC TCG AGG GGC GTC GTG
Asn Asp Gly Gly Ser Arg Ser Pro Ser Ser Glu Ser Ser Pro Gln His>

      260         270         280         290         300
CCC ACG CCC CCC GCC CGG CCC CGC CAC ATG CTG GGG CTC CCG TCA ACC
GGG TGC GGG GGG CGG GCC GGG GCG GTG TAC GAC CCC GAG GGC AGT TGG
Pro Thr Pro Pro Ala Arg Pro Arg His Met Leu Gly Leu Pro Ser Thr>

        310         320         330         340
CTG TTC ACA CCC CGC AGC ATG GAG AGC ATT GAG ATT GAC CAG AAG CTG
GAC AAG TGT GGG GCG TCG TAC CTC TCG TAA CTC TAA CTG GTC TTC GAC
Leu Phe Thr Pro Arg Ser Met Glu Ser Ile Glu Ile Asp Gln Lys Leu>

350         360         370         380         390
CAG GAG ATC ATG AAG CAG ACG GGC TAC CTG ACC ATC GGG GGC CAG CGC
GTC CTC TAG TAC TTC GTC TGC CCG ATG GAC TGG TAG CCC CCG GTC GCG
Gln Glu Ile Met Lys Gln Thr Gly Tyr Leu Thr Ile Gly Gly Gln Arg>

400         410         420         430         440
TAC CAG GCA GAA ATC AAC GAC CTG GAG AAC TTG GGC GAG ATG GGC AGC
ATG GTC CGT CTT TAG TTG CTG GAC CTC TTG AAC CCG CTC TAC CCG TCG
Tyr Gln Ala Glu Ile Asn Asp Leu Glu Asn Leu Gly Glu Met Gly Ser>
```

FIG. 12A

Human MKK7


```
     450         460         470         480         490
      *     *     *     *     *     *     *     *     *
GGC ACC TGC GGC CAG GTG TGG AAG ATG CGC TTC CGG AAG ACC GGC CAC
CCG TGG ACG CCG GTC CAC ACC TTC TAC GCG AAG GCC TTC TGG CCG GTG
Gly Thr Cys Gly Gln Val Trp Lys Met Arg Phe Arg Lys Thr Gly His>

       500         510         520         530         540
 *     *     *     *     *     *     *     *     *     *
GTC ATT GCC GTT AAG CAA ATG CGG CGC TCC GGG AAC AAG GAG GAG AAC
CAG TAA CGG CAA TTC GTT TAC GCC GCG AGG CCC TTG TTC CTC CTC TTG
Val Ile Ala Val Lys Gln Met Arg Arg Ser Gly Asn Lys Glu Glu Asn>

         550         560         570         580
    *     *     *     *     *     *     *     *     *
AAG CGC ATC CTC ATG GAC CTG GAT GTG GTG CTG AAG AGC CAC GAC TGC
TTC GCG TAG GAG TAC CTG GAC CTA CAC CAC GAC TTC TCG GTG CTG ACG
Lys Arg Ile Leu Met Asp Leu Asp Val Val Leu Lys Ser His Asp Cys>

590          600         610         620         630
 *     *     *     *     *     *     *     *     *     *
CCC TAC ATC GTG CAG TGC TTT GGG ACG TTC ATC ACC AAC ACG GAC GTC
GGG ATG TAG CAC GTC ACG AAA CCC TGC AAG TAG TGG TTG TGC CTG CAG
Pro Tyr Ile Val Gln Cys Phe Gly Thr Phe Ile Thr Asn Thr Asp Val>

640          650         660         670         680
 *     *     *     *     *     *     *     *     *     *
TTC ATC GCC ATG GAG CTC ATG GGC ACC TGC GCT GAG AAG CTC AAG AAG
AAG TAG CGG TAC CTC GAG TAC CCG TGG ACG CGA CTC TTC GAG TTC TTC
Phe Ile Ala Met Glu Leu Met Gly Thr Cys Ala Glu Lys Leu Lys Lys>

   690         700         710         720         730
    *     *     *     *     *     *     *     *     *
CGG ATG CAG GGC CCC ATC CCC GAG CGC ATT CTG GGC AAG ATG ACA GTG
GCC TAC GTC CCG GGG TAG GGG CTC GCG TAA GAC CCG TTC TAC TGT CAC
Arg Met Gln Gly Pro Ile Pro Glu Arg Ile Leu Gly Lys Met Thr Val>

       740         750         760         770         780
 *     *     *     *     *     *     *     *     *     *
GCG ATT GTG AAG GCG CTG TAC TAC CTG AAG GAG AAG CAC GGT GTC ATC
CGC TAA CAC TTC CGC GAC ATG ATG GAC TTC CTC TTC GTG CCA CAG TAG
Ala Ile Val Lys Ala Leu Tyr Tyr Leu Lys Glu Lys His Gly Val Ile>

         790         800         810         820
    *     *     *     *     *     *     *     *     *
CAC CGC GAC GTC AAG CCC TCC AAC ATC CTG CTG GAC GAG CGG GGC CAG
GTG GCG CTG CAG TTC GGG AGG TTG TAG GAC GAC CTG CTC GCC CCG GTC
His Arg Asp Val Lys Pro Ser Asn Ile Leu Leu Asp Glu Arg Gly Gln>

830          840
 *     *     *
ATC AAG CTC TGC GA (SEQ ID NO: 25)
TAG TTC GAG ACG CT
Ile Lys Leu Cys> (SEQ ID NO: 26)
```

FIG. 12B

Mouse MKK7c
Sequence Range: 1 to 1643

```
         10        20        30        40        50        60
AGCGCAGGCG CAGTGCGGTG TTTGTCTACC CCGGACTGAC GGGTGGCCTG GCGGTGAGCG
TCGCGTCCGC GTCACGCCAC AAACAGATGG GGCCTGACTG CCCACCGGAC CGCCACTCGC

         70        80          90         100         110
GCGGCAGCGG CGGCGGGGAA G ATG GCG GCG TCC TCC CTG GAG CAG AAG CTG
CGCCGTCGCC GCCGCCCCTT C TAC CGC CGC AGG AGG GAC CTC GTC TTC GAC
                        Met Ala Ala Ser Ser Leu Glu Gln Lys Leu>

       120         130         140         150
TCC CGC CTG GAA GCC AAG CTG AAG CAG GAG AAC CGT GAG GCC CGC AGG
AGG GCG GAC CTT CGG TTC GAC TTC GTC CTC TTG GCA CTC CGG GCG TCC
Ser Arg Leu Glu Ala Lys Leu Lys Gln Glu Asn Arg Glu Ala Arg Arg>

160        170         180         190         200
AGG ATC GAC CTC AAC TTG GAT ATC AGC CCA CAG CGG CCC AGG CCC ACC
TCC TAG CTG GAG TTG AAC CTA TAG TCG GGT GTC GCC GGG TCC GGG TGG
Arg Ile Asp Leu Asn Leu Asp Ile Ser Pro Gln Arg Pro Arg Pro Thr>

210         220         230         240         250
CTG CAA CTC CCA CTG GCC AAC GAT GGG GGC AGC CGC TCA CCA TCC TCA
GAC GTT GAG GGT GAC CGG TTG CTA CCC CCG TCG GCG AGT GGT AGG AGT
Leu Gln Leu Pro Leu Ala Asn Asp Gly Gly Ser Arg Ser Pro Ser Ser>

    260         270         280         290         300
GAG AGC TCC CCA CAG CAC CCT ACA CCC CCC ACC CGG CCC CGC CAC ATG
CTC TCG AGG GGT GTC GTG GGA TGT GGG GGG TGG GCC GGG GCG GTG TAC
Glu Ser Ser Pro Gln His Pro Thr Pro Pro Thr Arg Pro Arg His Met>

      310         320         330         340         350
CTG GGG CTC CCA TCA ACC TTG TTC ACA CCG CGC AGT ATG GAG AGC ATC
GAC CCC GAG GGT AGT TGG AAC AAG TGT GGC GCG TCA TAC CTC TCG TAG
Leu Gly Leu Pro Ser Thr Leu Phe Thr Pro Arg Ser Met Glu Ser Ile>

        360         370         380         390
GAG ATT GAC CAG AAG CTG CAG GAG ATC ATG AAG CAG ACA GGG TAC CTG
CTC TAA CTG GTC TTC GAC GTC CTC TAG TAC TTC GTC TGT CCC ATG GAC
Glu Ile Asp Gln Lys Leu Gln Glu Ile Met Lys Gln Thr Gly Tyr Leu>

400         410         420         430         440
ACT ATC GGG GGC CAG CGT TAT CAG GCA GAA ATC AAT GAC TTG GAG AAC
TGA TAG CCC CCG GTC GCA ATA GTC CGT CTT TAG TTA CTG AAC CTC TTG
Thr Ile Gly Gly Gln Arg Tyr Gln Ala Glu Ile Asn Asp Leu Glu Asn>
```

FIG. 13A

Mouse MKK7c

```
450         460         470         480         490
 *     *     *     *     *     *     *     *     *     *
TTG GGT GAG ATG GGC AGT GGT ACC TGT GGT CAG GTG TGG AAG ATG CGG
AAC CCA CTC TAC CCG TCA CCA TGG ACA CCA GTC CAC ACC TTC TAC GCC
Leu Gly Glu Met Gly Ser Gly Thr Cys Gly Gln Val Trp Lys Met Arg>

  500         510         520         530         540
   *     *     *     *     *     *     *     *     *
TTC CGG AAG ACA GGC CAC ATC ATT GCT GTT AAG CAA ATG CGG CGC TCT
AAG GCC TTC TGT CCG GTG TAG TAA CGA CAA TTC GTT TAC GCC GCG AGA
Phe Arg Lys Thr Gly His Ile Ile Ala Val Lys Gln Met Arg Arg Ser>

      550         560         570         580         590
 *     *     *     *     *     *     *     *     *     *
GGG AAC AAG GAA GAG AAT AAG CGC ATT TTG ATG GAC CTG GAT GTA GTA
CCC TTG TTC CTT CTC TTA TTC GCG TAA AAC TAC CTG GAC CTA CAT CAT
Gly Asn Lys Glu Glu Asn Lys Arg Ile Leu Met Asp Leu Asp Val Val>

        600         610         620         630
   *     *     *     *     *     *     *     *     *
CTC AAG AGC CAT GAC TGC CCT TAC ATC GTT CAG TGC TTT GGC ACC TTC
GAG TTC TCG GTA CTG ACG GGA ATG TAG CAA GTC ACG AAA CCG TGG AAG
Leu Lys Ser His Asp Cys Pro Tyr Ile Val Gln Cys Phe Gly Thr Phe>

640         650         660         670         680
 *     *     *     *     *     *     *     *     *     *
ATC ACC AAC ACA GAC GTC TTT ATT GCC ATG GAG CTC ATG GGC ACA TGT
TAG TGG TTG TGT CTG CAG AAA TAA CGG TAC CTC GAG TAC CCG TGT ACA
Ile Thr Asn Thr Asp Val Phe Ile Ala Met Glu Leu Met Gly Thr Cys>

690         700         710         720         730
 *     *     *     *     *     *     *     *     *     *
GCA GAG AAG CTG AAG AAA CGA ATG CAG GGC CCC ATT CCA GAG CGA ATC
CGT CTC TTC GAC TTC TTT GCT TAC GTC CCG GGG TAA GGT CTC GCT TAG
Ala Glu Lys Leu Lys Lys Arg Met Gln Gly Pro Ile Pro Glu Arg Ile>

    740         750         760         770         780
     *     *     *     *     *     *     *     *     *
CTG GGC AAG ATG ACT GTG GCG ATT GTG AAA GCA CTG TAC TAT CTG AAG
GAC CCG TTC TAC TGA CAC CGC TAA CAC TTT CGT GAC ATG ATA GAC TTC
Leu Gly Lys Met Thr Val Ala Ile Val Lys Ala Leu Tyr Tyr Leu Lys>

      790         800         810         820         830
 *     *     *     *     *     *     *     *     *     *
GAG AAG CAT GGC GTC ATC CAT CGC GAT GTC AAA CCC TCC AAC ATC CTG
CTC TTC GTA CCG CAG TAG GTA GCG CTA CAG TTT GGG AGG TTG TAG GAC
Glu Lys His Gly Val Ile His Arg Asp Val Lys Pro Ser Asn Ile Leu>

        840         850         860         870
   *     *     *     *     *     *     *     *     *
CTA GAT GAG CGG GGC CAG ATC AAG CTC TGT GAC TTT GGC ATC AGT GGC
GAT CTA CTC GCC CCG GTC TAG TTC GAG ACA CTG AAA CCG TAG TCA CCG
Leu Asp Glu Arg Gly Gln Ile Lys Leu Cys Asp Phe Gly Ile Ser Gly>
```

FIG. 13B

Mouse MKK7c

```
880         890         900         910         920
 *     *     *     *     *     *     *     *     *     *
CGC CTT GTT GAC TCC AAA GCC AAA ACA CGG AGT GCT GGC TGT GCT GCC
GCG GAA CAA CTG AGG TTT CGG TTT TGT GCC TCA CGA CCG ACA CGA CGG
Arg Leu Val Asp Ser Lys Ala Lys Thr Arg Ser Ala Gly Cys Ala Ala>

930         940         950         960         970
 *     *     *     *     *     *     *     *     *     *
TAT ATG GCT CCC GAG CGC ATC GAC CCT CCA GAT CCC ACC AAG CCT GAC
ATA TAC CGA GGG CTC GCG TAG CTG GGA GGT CTA GGG TGG TTC GGA CTG
Tyr Met Ala Pro Glu Arg Ile Asp Pro Pro Asp Pro Thr Lys Pro Asp>

    980         990         1000        1010        1020
     *     *     *     *     *     *     *     *     *
TAT GAC ATC CGA GCT GAT GTG TGG AGC CTG GGC ATC TCA CTG GTG GAG
ATA CTG TAG GCT CGA CTA CAC ACC TCG GAC CCG TAG AGT GAC CAC CTC
Tyr Asp Ile Arg Ala Asp Val Trp Ser Leu Gly Ile Ser Leu Val Glu>

     1030        1040        1050        1060        1070
 *     *     *     *     *     *     *     *     *     *
CTG GCA ACA GGA CAG TTC CCC TAT AAG AAC TGC AAG ACG GAC TTT GAG
GAC CGT TGT CCT GTC AAG GGG ATA TTC TTG ACG TTC TGC CTG AAA CTC
Leu Ala Thr Gly Gln Phe Pro Tyr Lys Asn Cys Lys Thr Asp Phe Glu>

        1080        1090        1100        1110
     *     *     *     *     *     *     *     *     *
GTC CTC ACC AAA GTC CTA CAG GAA GAG CCC CCA CTC CTG CCT GGT CAC
CAG GAG TGG TTT CAG GAT GTC CTT CTC GGG GGT GAG GAC GGA CCA GTG
Val Leu Thr Lys Val Leu Gln Glu Glu Pro Pro Leu Leu Pro Gly His>

1120        1130        1140        1150        1160
 *     *     *     *     *     *     *     *     *     *
ATG GGC TTC TCA GGG GAC TTC CAG TCA TTT GTC AAA GAC TGC CTT ACT
TAC CCG AAG AGT CCC CTG AAG GTC AGT AAA CAG TTT CTG ACG GAA TGA
Met Gly Phe Ser Gly Asp Phe Gln Ser Phe Val Lys Asp Cys Leu Thr>

1170        1180        1190        1200        1210
 *     *     *     *     *     *     *     *     *     *
AAA GAT CAC AGG AAG AGA CCA AAG TAT AAT AAG CTA CTT GAA CAC AGC
TTT CTA GTG TCC TTC TCT GGT TTC ATA TTA TTC GAT GAA CTT GTG TCG
Lys Asp His Arg Lys Arg Pro Lys Tyr Asn Lys Leu Leu Glu His Ser>

 1220        1230        1240        1250        1260
  *     *     *     *     *     *     *     *     *
TTC ATC AAG CAC TAT GAG ATA CTC GAG GTG GAT GTC GCG TCC TGG TTT
AAG TAG TTC GTG ATA CTC TAT GAG CTC CAC CTA CAG CGC AGG ACC AAA
Phe Ile Lys His Tyr Glu Ile Leu Glu Val Asp Val Ala Ser Trp Phe>

     1270        1280        1290        1300        1310
 *     *     *     *     *     *     *     *     *     *
AAG GAT GTC ATG GCG AAG ACC GAG TCC CCA AGG ACT AGT GGA GTC CTG
TTC CTA CAG TAC CGC TTC TGG CTC AGG GGT TCC TGA TCA CCT CAG GAC
```

FIG. 13C

Mouse MKK7c

```
Lys Asp Val Met Ala Lys Thr Glu Ser Pro Arg Thr Ser Gly Val Leu>

        1320           1330          1340        1350        1360
     *     *        *     *     *      *     *     *     *     *
AGT CAG CAC CAT CTG CCC TTC TTC AGG TA GCCTCATGGC AGCGGCCAGC
TCA GTC GTG GTA GAC GGG AAG AAG TCC AT CGGAGTACCG TCGCCGGTCG
Ser Gln His His Leu Pro Phe Phe Arg> (SEQ ID NO: 28)

       1370       1380       1390       1400       1410       1420
     *    *     *    *     *    *     *    *     *    *     *    *
CCCGCAGGGG CCCCGGGCCA CGGCCACCGA CCCCCCCCCC AACCTGGCCA ACCCAGCTGC
GGGCGTCCCC GGGGCCCGGT GCCGGTGGCT GGGGGGGGGG TTGGACCGGT TGGGTCGACG

       1430       1440       1450       1460       1470       1480
     *    *     *    *     *    *     *    *     *    *     *    *
CCATCAGGGG ACCTGGGACC TGGACGACTG CCAAGGACTG AGGACAGAAA GTAGGGGGTT
GGTAGTCCCC TGGACCCTGG ACCTGCTGAC GGTTCCTGAC TCCTGTCTTT CATCCCCCAA

       1490       1500       1510       1520       1530       1540
     *    *     *    *     *    *     *    *     *    *     *    *
CCCATCCAGC TCTGACTCCC TGCCTACCAG CTGTGGACAA AAGGGCATGC TGGTTCCTAA
GGGTAGGTCG AGACTGAGGG ACGGATGGTC GACACCTGTT TTCCCGTACG ACCAAGGATT

       1550       1560       1570       1580       1590       1600
     *    *     *    *     *    *     *    *     *    *     *    *
TCCCTCCCAC TCTGGGGTCA GCCAGCAGTG TGAGCCCCAT CCCACCCCGA CAGACACTGT
AGGGAGGGTG AGACCCCAGT CGGTCGTCAC ACTCGGGGTA GGGTGGGGCT GTCTGTGACA

       1610       1620       1630       1640
     *    *     *    *     *    *     *    *
GAACGGAAGA CAGCAGGCCA AAAAAAAAAA AAAAAAAAAA AAA (SEQ ID NO: 27)
CTTGCCTTCT GTCGTCCGGT TTTTTTTTTT TTTTTTTTTT TTT
```

FIG. 13D

MKK7d 46/54

Sequence Range: 1 to 1578

```
         10         20         30         40         50         60
GGAAAGGCAG CCTCCTGTAG GTGAAAATTC TGTTCACTAC CTGGCCACCT GGCCTGACTG
CCTTTCCGTC GGAGGACATC CACTTTTAAG ACAAGTGATG GACCGGTGGA CCGGACTGAC

         70         80         90        100        110        120
ACCTTCACAG CTTGATCATC TTCCTGAAGA GGCATTCAGG ATTCCCTCCA TCCCTACCCC
TGGAAGTGTC GAACTAGTAG AAGGACTTCT CCGTAAGTCC TAAGGGAGGT AGGGATGGGG

        130        140        150        160        170        180
TTCTGGACAA AGTCTTCCAC GTTTCCTTCC TGGGAGTTTC TTCCAGGAAC TGGAGATACC
AAGACCTGTT TCAGAAGGTG CAAAGGAAGG ACCCTCAAAG AAGGTCCTTG ACCTCTATGG

        190        200        210        220        230        240
CAGAGCCCTG CAACTCCCAC TGGCCAACGA TGGGGGCAGC CGCTCACCAT CCTCAGAGAG
GTCTCGGGAC GTTGAGGGTG ACCGGTTGCT ACCCCCGTCG GCGAGTGGTA GGAGTCTCTC

        250        260        270        280           290
CTCCCCACAG CACCCTACAC CCCCCACCCG GCCCCGCCAC ATG CTG GGG CTC CCA
GAGGGGTGTC GTGGGATGTG GGGGGTGGGC CGGGGCGGTG TAC GAC CCC GAG GGT
                                            Met Leu Gly Leu Pro>

    300         310            320            330            340
TCA ACC TTG TTC ACA CCG CGC AGT ATG GAG AGC ATC GAG ATT GAC CAG
AGT TGG AAC AAG TGT GGC GCG TCA TAC CTC TCG TAG CTC TAA CTG GTC
Ser Thr Leu Phe Thr Pro Arg Ser Met Glu Ser Ile Glu Ile Asp Gln>

      350            360            370            380            390
AAG CTG CAG GAG ATC ATG AAG CAG ACA GGG TAC CTG ACT ATC GGG GGC
TTC GAC GTC CTC TAG TAC TTC GTC TGT CCC ATG GAC TGA TAG CCC CCG
Lys Leu Gln Glu Ile Met Lys Gln Thr Gly Tyr Leu Thr Ile Gly Gly>

        400            410            420            430
CAG CGT TAT CAG GCA GAA ATC AAT GAC TTG GAG AAC TTG GGT GAG ATG
GTC GCA ATA GTC CGT CTT TAG TTA CTG AAC CTC TTG AAC CCA CTC TAC
Gln Arg Tyr Gln Ala Glu Ile Asn Asp Leu Glu Asn Leu Gly Glu Met>

440            450            460            470            480
GGC AGT GGT ACC TGT GGT CAG GTG TGG AAG ATG CGG TTC CGG AAG ACA
CCG TCA CCA TGG ACA CCA GTC CAC ACC TTC TAC GCC AAG GCC TTC TGT
Gly Ser Gly Thr Cys Gly Gln Val Trp Lys Met Arg Phe Arg Lys Thr>

490            500            510            520            530
GGC CAC ATC ATT GCT GTT AAG CAA ATG CGG CGC TCT GGG AAC AAG GAA
CCG GTG TAG TAA CGA CAA TTC GTT TAC GCC GCG AGA CCC TTG TTC CTT
Gly His Ile Ile Ala Val Lys Gln Met Arg Arg Ser Gly Asn Lys Glu>
```

FIG. 14A

MKK7d

```
    540         550          560          570          580
GAG AAT AAG CGC ATT TTG ATG GAC CTG GAT GTA GTA CTC AAG AGC CAT
CTC TTA TTC GCG TAA AAC TAC CTG GAC CTA CAT CAT GAG TTC TCG GTA
Glu Asn Lys Arg Ile Leu Met Asp Leu Asp Val Val Leu Lys Ser His>

       590          600          610          620          630
GAC TGC CCT TAC ATC GTT CAG TGC TTT GGC ACC TTC ATC ACC AAC ACA
CTG ACG GGA ATG TAG CAA GTC ACG AAA CCG TGG AAG TAG TGG TTG TGT
Asp Cys Pro Tyr Ile Val Gln Cys Phe Gly Thr Phe Ile Thr Asn Thr>

          640          650          660          670
GAC GTC TTT ATT GCC ATG GAG CTC ATG GGC ACA TGT GCA GAG AAG CTG
CTG CAG AAA TAA CGG TAC CTC GAG TAC CCG TGT ACA CGT CTC TTC GAC
Asp Val Phe Ile Ala Met Glu Leu Met Gly Thr Cys Ala Glu Lys Leu>

680          690          700          710          720
AAG AAA CGA ATG CAG GGC CCC ATT CCA GAG CGA ATC CTG GGC AAG ATG
TTC TTT GCT TAC GTC CCG GGG TAA GGT CTC GCT TAG GAC CCG TTC TAC
Lys Lys Arg Met Gln Gly Pro Ile Pro Glu Arg Ile Leu Gly Lys Met>

730          740          750          760          770
ACT GTG GCG ATT GTG AAA GCA CTG TAC TAT CTG AAG GAG AAG CAT GGC
TGA CAC CGC TAA CAC TTT CGT GAC ATG ATA GAC TTC CTC TTC GTA CCG
Thr Val Ala Ile Val Lys Ala Leu Tyr Tyr Leu Lys Glu Lys His Gly>

    780          790          800          810          820
GTC ATC CAT CGC GAT GTC AAA CCC TCC AAC ATC CTG CTA GAT GAG CGG
CAG TAG GTA GCG CTA CAG TTT GGG AGG TTG TAG GAC GAT CTA CTC GCC
Val Ile His Arg Asp Val Lys Pro Ser Asn Ile Leu Leu Asp Glu Arg>

       830          840          850          860          870
GGC CAG ATC AAG CTC TGT GAC TTT GGC ATC AGT GGC CGC CTT GTT GAC
CCG GTC TAG TTC GAG ACA CTG AAA CCG TAG TCA CCG GCG GAA CAA CTG
Gly Gln Ile Lys Leu Cys Asp Phe Gly Ile Ser Gly Arg Leu Val Asp>

          880          890          900          910
TCC AAA GCC AAA ACA CGG AGT GCT GGC TGT GCT GCC TAT ATG GCT CCC
AGG TTT CGG TTT TGT GCC TCA CGA CCG ACA CGA CGG ATA TAC CGA GGG
Ser Lys Ala Lys Thr Arg Ser Ala Gly Cys Ala Ala Tyr Met Ala Pro>

920          930          940          950          960
GAG CGC ATC GAC CCT CCA GAT CCC ACC AAG CCT GAC TAT GAC ATC CGA
CTC GCG TAG CTG GGA GGT CTA GGG TGG TTC GGA CTG ATA CTG TAG GCT
```

FIG. 14B

MKK7d 48/54

```
Glu Arg Ile Asp Pro Pro Asp Pro Thr Lys Pro Asp Tyr Asp Ile Arg>

970         980         990         1000        1010
GCT GAT GTG TGG AGC CTG GGC ATC TCA CTG GTG GAG CTG GCA ACA GGA
CGA CTA CAC ACC TCG GAC CCG TAG AGT GAC CAC CTC GAC CGT TGT CCT
Ala Asp Val Trp Ser Leu Gly Ile Ser Leu Val Glu Leu Ala Thr Gly>

1020        1030        1040        1050        1060
CAG TTC CCC TAT AAG AAC TGC AAG ACG GAC TTT GAG GTC CTC ACC AAA
GTC AAG GGG ATA TTC TTG ACG TTC TGC CTG AAA CTC CAG GAG TGG TTT
Gln Phe Pro Tyr Lys Asn Cys Lys Thr Asp Phe Glu Val Leu Thr Lys>

1070        1080        1090        1100        1110
GTC CTA CAG GAA GAG CCC CCA CTC CTG CCT GGT CAC ATG GGC TTC TCA
CAG GAT GTC CTT CTC GGG GGT GAG GAC GGA CCA GTG TAC CCG AAG AGT
Val Leu Gln Glu Glu Pro Pro Leu Leu Pro Gly His Met Gly Phe Ser>

1120        1130        1140        1150
GGG GAC TTC CAG TCA TTT GTC AAA GAC TGC CTT ACT AAA GAT CAC AGG
CCC CTG AAG GTC AGT AAA CAG TTT CTG ACG GAA TGA TTT CTA GTG TCC
Gly Asp Phe Gln Ser Phe Val Lys Asp Cys Leu Thr Lys Asp His Arg>

1160        1170        1180        1190        1200
AAG AGA CCA AAG TAT AAT AAG CTA CTT GAA CAC AGC TTC ATC ATC AAG
TTC TCT GGT TTC ATA TTA TTC GAT GAA CTT GTG TCG AAG TAG TAG TTC
Lys Arg Pro Lys Tyr Asn Lys Leu Leu Glu His Ser Phe Ile Ile Lys>

1210        1220        1230        1240        1250
CAC TAT GAG ATA CTC GAG GTG GAT GTC GCG TCC TGG TTT AAG GAT GTC
GTG ATA CTC TAT GAG CTC CAC CTA CAG CGC AGG ACC AAA TTC CTA CAG
His Tyr Glu Ile Leu Glu Val Asp Val Ala Ser Trp Phe Lys Asp Val>

1260        1270        1280        1290        1300
ATG GCG AAG ACC GAG TCC CCA AGG ACT AGT GGA GTC CTG AGT CAG CAC
TAC CGC TTC TGG CTC AGG GGT TCC TGA TCA CCT CAG GAC TCA GTC GTG
Met Ala Lys Thr Glu Ser Pro Arg Thr Ser Gly Val Leu Ser Gln His>

1310        1320        1330        1340        1350
CAT CTG CCC TTC TTC AGT GGG AGT CTG GAG GAG TCT CCC ACT TCC CCA
GTA GAC GGG AAG AAG TCA CCC TCA GAC CTC CTC AGA GGG TGA AGG GGT
His Leu Pro Phe Phe Ser Gly Ser Leu Glu Glu Ser Pro Thr Ser Pro>

1360        1370        1380        1390
CCT TCT CCC AAG TCC TTC CCT CTG TCA CCA GCC ATC CCT CAG GCC CAG
```

FIG. 14C

MKK7d 49/54

```
GGA AGA GGG TTC AGG AAG GGA GAC AGT GGT CGG TAG GGA GTC CGG GTC
Pro Ser Pro Lys Ser Phe Pro Leu Ser Pro Ala Ile Pro Gln Ala Gln>

1400          1410          1420          1430          1440          1450
  *       *       *       *       *       *       *       *       *       *
GCA GAG TGG GTC TCG GGC AGG TAGGGACCTG GAGTGGCCTG GTCCCACCCT
CGT CTC ACC CAG AGC CCG TCC ATCCCTGGAC CTCACCGGAC CAGGGTGGGA
Ala Glu Trp Val Ser Gly Arg>  (SEQ ID NO: 30)

        1460          1470          1480          1490          1500          1510
      *       *       *       *       *       *       *       *       *       *
CTGACCTCCT CCTCAGGCCA CCAGTGTTGC CCTCTTCCCT TTTTAAAACA AAATACCCTT
GACTGGAGGA GGAGTCCGGT GGTCACAACG GGAGAAGGGA AAAATTTTGT TTTATGGGAA

        1520          1530          1540          1550          1560          1570
      *       *       *       *       *       *       *       *       *       *
GTTTGTAAAT CCTTAGACGC TTGAGAATAA AACCCTTCCC TTTTCTTCCG AAAAAAAAAA
CAAACATTTA GGAATCTGCG AACTCTTATT TTGGGAAGGG AAAAGAAGGC TTTTTTTTTT

      *
AAAAAAAA  (SEQ ID NO: 29)
TTTTTTTT
```

FIG. 14D

MKK7e
Sequence Range: 1 to 1598

```
           10        20        30        40        50        60
 AGCGCAGGCG CAGTGCGGTG TTTGTCTACC CCGGACTGAC GGGTGGCCTG GCGGTGAGCG
 TCGCGTCCGC GTCACGCCAC AAACAGATGG GGCCTGACTG CCCACCGGAC CGCCACTCGC

           70        80          90       100       110
 GCGGCAGCGG CGGCGGGGAA G ATG GCG GCG TCC TCC CTG GAG CAG AAG CTG
 CGCCGTCGCC GCCGCCCCTT C TAC CGC CGC AGG AGG GAC CTC GTC TTC GAC
                         Met Ala Ala Ser Ser Leu Glu Gln Lys Leu>

         120         130         140         150
 TCC CGC CTG GAA GCC AAG CTG AAG CAG GAG AAC CGT GAG GCC CGC AGG
 AGG GCG GAC CTT CGG TTC GAC TTC GTC CTC TTG GCA CTC CGG GCG TCC
 Ser Arg Leu Glu Ala Lys Leu Lys Gln Glu Asn Arg Glu Ala Arg Arg>

160         170         180         190         200
 AGG ATC GAC CTC AAC TTG GAT ATC AGC CCA CAG CGG CCC AGG CCC ACC
 TCC TAG CTG GAG TTG AAC CTA TAG TCG GGT GTC GCC GGG TCC GGG TGG
 Arg Ile Asp Leu Asn Leu Asp Ile Ser Pro Gln Arg Pro Arg Pro Thr>

 210         220         230         240         250
 CTG CAA CTC CCA CTG GCC AAC GAT GGG GGC AGC CGC TCA CCA TCC TCA
 GAC GTT GAG GGT GAC CGG TTG CTA CCC CCG TCG GCG AGT GGT AGG AGT
 Leu Gln Leu Pro Leu Ala Asn Asp Gly Gly Ser Arg Ser Pro Ser Ser>

     260         270         280         290         300
 GAG AGC TCC CCA CAG CAC CCT ACA CCC CCC ACC CGG CCC CGC CAC ATG
 CTC TCG AGG GGT GTC GTG GGA TGT GGG GGG TGG GCC GGG GCG GTG TAC
 Glu Ser Ser Pro Gln His Pro Thr Pro Pro Thr Arg Pro Arg His Met>

       310         320         330         340         350
 CTG GGG CTC CCA TCA ACC TTG TTC ACA CCG CGC AGT ATG GAG AGC ATC
 GAC CCC GAG GGT AGT TGG AAC AAG TGT GGC GCG TCA TAC CTC TCG TAG
 Leu Gly Leu Pro Ser Thr Leu Phe Thr Pro Arg Ser Met Glu Ser Ile>

         360         370         380         390
 GAG ATT GAC CAG AAG CTG CAG GAG ATC ATG AAG CAG ACA GGG TAC CTG
 CTC TAA CTG GTC TTC GAC GTC CTC TAG TAC TTC GTC TGT CCC ATG GAC
 Glu Ile Asp Gln Lys Leu Gln Glu Ile Met Lys Gln Thr Gly Tyr Leu>

400         410         420         430         440
 ACT ATC GGG GGC CAG CGT TAT CAG GCA GAA ATC AAT GAC TTG GAG AAC
 TGA TAG CCC CCG GTC GCA ATA GTC CGT CTT TAG TTA CTG AAC CTC TTG
 Thr Ile Gly Gly Gln Arg Tyr Gln Ala Glu Ile Asn Asp Leu Glu Asn>
```

FIG. 15A

Mouse MKK7e


```
450       460       470       480       490
TTG GGT GAG ATG GGC AGT GGT ACC TGT GGT CAG GTG TGG AAG ATG CGG
AAC CCA CTC TAC CCG TCA CCA TGG ACA CCA GTC CAC ACC TTC TAC GCC
Leu Gly Glu Met Gly Ser Gly Thr Cys Gly Gln Val Trp Lys Met Arg>

   500       510       520       530       540
TTC CGG AAG ACA GGC CAC ATC ATT GCT GTT AAG CAA ATG CGG CGC TCT
AAG GCC TTC TGT CCG GTG TAG TAA CGA CAA TTC GTT TAC GCC GCG AGA
Phe Arg Lys Thr Gly His Ile Ile Ala Val Lys Gln Met Arg Arg Ser>

      550       560       570       580       590
GGG AAC AAG GAA GAG AAT AAG CGC ATT TTG ATG GAC CTG GAT GTA GTA
CCC TTG TTC CTT CTC TTA TTC GCG TAA AAC TAC CTG GAC CTA CAT CAT
Gly Asn Lys Glu Glu Asn Lys Arg Ile Leu Met Asp Leu Asp Val Val>

         600       610       620       630
CTC AAG AGC CAT GAC TGC CCT TAC ATC GTT CAG TGC TTT GGC ACC TTC
GAG TTC TCG GTA CTG ACG GGA ATG TAG CAA GTC ACG AAA CCG TGG AAG
Leu Lys Ser His Asp Cys Pro Tyr Ile Val Gln Cys Phe Gly Thr Phe>

640       650       660       670       680
ATC ACC AAC ACA GAC GTC TTT ATT GCC ATG GAG CTC ATG GGC ACA TGT
TAG TGG TTG TGT CTG CAG AAA TAA CGG TAC CTC GAG TAC CCG TGT ACA
Ile Thr Asn Thr Asp Val Phe Ile Ala Met Glu Leu Met Gly Thr Cys>

690       700       710       720       730
GCA GAG AAG CTG AAG AAA CGA ATG CAG GGC CCC ATT CCA GAG CGA ATC
CGT CTC TTC GAC TTC TTT GCT TAC GTC CCG GGG TAA GGT CTC GCT TAG
Ala Glu Lys Leu Lys Lys Arg Met Gln Gly Pro Ile Pro Glu Arg Ile>

   740       750       760       770       780
CTG GGC AAG ATG ACT GTG GCG ATT GTG AAA GCA CTG TAC TAT CTG AAG
GAC CCG TTC TAC TGA CAC CGC TAA CAC TTT CGT GAC ATG ATA GAC TTC
Leu Gly Lys Met Thr Val Ala Ile Val Lys Ala Leu Tyr Tyr Leu Lys>

      790       800       810       820       830
GAG AAG CAT GGC GTC ATC CAT CGC GAT GTC AAA CCC TCC AAC ATC CTG
CTC TTC GTA CCG CAG TAG GTA GCG CTA CAG TTT GGG AGG TTG TAG GAC
Glu Lys His Gly Val Ile His Arg Asp Val Lys Pro Ser Asn Ile Leu>

         840       850       860       870
CTA GAT GAG CGG GGC CAG ATC AAG CTC TGT GAC TTT GGC ATC AGT GGC
GAT CTA CTC GCC CCG GTC TAG TTC GAG ACA CTG AAA CCG TAG TCA CCG
Leu Asp Glu Arg Gly Gln Ile Lys Leu Cys Asp Phe Gly Ile Ser Gly>
```

FIG. 15B

52/54

Mouse MKK7e

```
880       890       900       910       920
CGC CTT GTT GAC TCC AAA GCC AAA ACA CGG AGT GCT GGC TGT GCT GCC
GCG GAA CAA CTG AGG TTT CGG TTT TGT GCC TCA CGA CCG ACA CGA CGG
Arg Leu Val Asp Ser Lys Ala Lys Thr Arg Ser Ala Gly Cys Ala Ala>

930       940       950       960       970
TAT ATG GCT CCC GAG CGC ATC GAC CCT CCA GAT CCC ACC AAG CCT GAC
ATA TAC CGA GGG CTC GCG TAG CTG GGA GGT CTA GGG TGG TTC GGA CTG
Tyr Met Ala Pro Glu Arg Ile Asp Pro Pro Asp Pro Thr Lys Pro Asp>

980       990       1000      1010      1020
TAT GAC ATC CGA GCT GAT GTG TGG AGC CTG GGC ATC TCA CTG GTG GAG
ATA CTG TAG GCT CGA CTA CAC ACC TCG GAC CCG TAG AGT GAC CAC CTC
Tyr Asp Ile Arg Ala Asp Val Trp Ser Leu Gly Ile Ser Leu Val Glu>

1030      1040      1050      1060      1070
CTG GCA ACA GGA CAG TTC CCC TAT AAG AAC TGC AAG ACG GAC TTT GAG
GAC CGT TGT CCT GTC AAG GGG ATA TTC TTG ACG TTC TGC CTG AAA CTC
Leu Ala Thr Gly Gln Phe Pro Tyr Lys Asn Cys Lys Thr Asp Phe Glu>

1080      1090      1100      1110
GTC CTC ACC AAA GTC CTA CAG GAA GAG CCC CCA CTC CTG CCT GGT CAC
CAG GAG TGG TTT CAG GAT GTC CTT CTC GGG GGT GAG GAC GGA CCA GTG
Val Leu Thr Lys Val Leu Gln Glu Glu Pro Pro Leu Leu Pro Gly His>

1120      1130      1140      1150      1160
ATG GGC TTC TCA GGG GAC TTC CAG TCA TTT GTC AAA GAC TGC CTT ACT
TAC CCG AAG AGT CCC CTG AAG GTC AGT AAA CAG TTT CTG ACG GAA TGA
Met Gly Phe Ser Gly Asp Phe Gln Ser Phe Val Lys Asp Cys Leu Thr>

1170      1180      1190      1200      1210
AAA GAT CAC AGG AAG AGA CCA AAG TAT AAT AAG CTA CTT GAA CAC AGC
TTT CTA GTG TCC TTC TCT GGT TTC ATA TTA TTC GAT GAA CTT GTG TCG
Lys Asp His Arg Lys Arg Pro Lys Tyr Asn Lys Leu Leu Glu His Ser>

1220      1230      1240      1250      1260
TTC ATC ATC AAG CAC TAT GAG ATA CTC GAG GTG GAT GTC GCG TCC TGG
AAG TAG TAG TTC GTG ATA CTC TAT GAG CTC CAC CTA CAG CGC AGG ACC
Phe Ile Ile Lys His Tyr Glu Ile Leu Glu Val Asp Val Ala Ser Trp>

1270      1280      1290      1300      1310
TTT AAG GAT GTC ATG GCG AAG ACC GAG TCC CCA AGG ACT AGT GGA GTC
AAA TTC CTA CAG TAC CGC TTC TGG CTC AGG GGT TCC TGA TCA CCT CAG
```

FIG. 15C

Mouse MKK7e

```
Phe Lys Asp Val Met Ala Lys Thr Glu Ser Pro Arg Thr Ser Gly Val>

         1320          1330          1340          1350
        *      *     *     *     *     *     *     *     *
CTG AGT CAG CAC CAT CTG CCC TTC TTC AGT GGG AGT CTG GAG GAG TCT
GAC TCA GTC GTG GTA GAC GGG AAG AAG TCA CCC TCA GAC CTC CTC AGA
Leu Ser Gln His His Leu Pro Phe Phe Ser Gly Ser Leu Glu Glu Ser>

1360           1370          1380          1390          1400
   *     *     *     *     *     *     *     *     *     *
CCC ACT TCC CCA CCT TCT CCC AAG TCC TTC CCT CTG TCA CCA GCC ATC
GGG TGA AGG GGT GGA AGA GGG TTC AGG AAG GGA GAC AGT GGT CGG TAG
Pro Thr Ser Pro Pro Ser Pro Lys Ser Phe Pro Leu Ser Pro Ala Ile>

 1410          1420          1430          1440       1450       1460
    *     *     *     *     *     *     *     *     *     *     *
CCT CAG GCC CAG GCA GAG TGG GTC TCG GGC AGG TAGGGACCTG GAGTGGCCTG
GGA GTC CGG GTC CGT CTC ACC CAG AGC CCG TCC ATCCCTGGAC CTCACCGGAC
Pro Gln Ala Gln Ala Glu Trp Val Ser Gly Arg> (SEQ ID NO: 32)

       1470       1480       1490       1500       1510       1520
    *     *     *     *     *     *     *     *     *     *     *     *
GTCCCACCCT CTGACCTCCT CCTCAGGCCA CCAGTGTTGC CCTCTTCCCT TTTTAAAACA
CAGGGTGGGA GACTGGAGGA GGAGTCCGGT GGTCACAACG GGAGAAGGGA AAAATTTTGT

       1530       1540       1550       1560       1570       1580
    *     *     *     *     *     *     *     *     *     *     *     *
AAATACCCTT GTTTGTAAAT CCTTAGACGC TTGAGAATAA AACCCTTCCC TTTTCTTCCG
TTTATGGGAA CAAACATTTA GGAATCTGCG AACTCTTATT TTGGGAAGGG AAAAGAAGGC

       1590
    *     *     *
AAAAAAAAAA AAAAAAAA (SEQ ID NO: 31)
TTTTTTTTTT TTTTTTTT
```

FIG. 15D

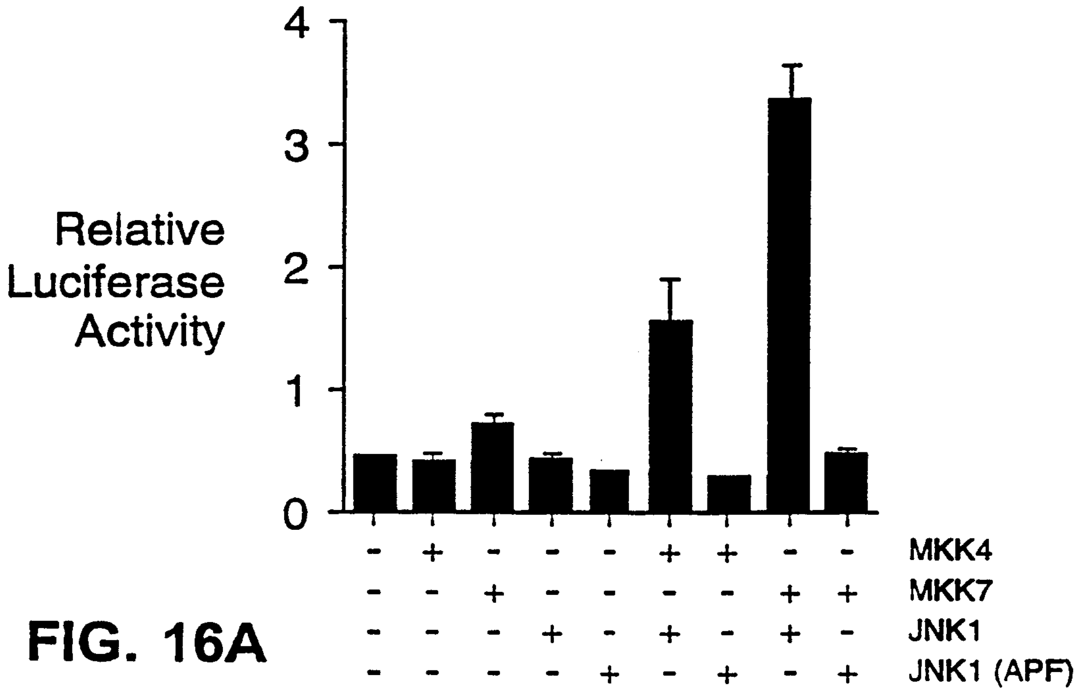

FIG. 16A

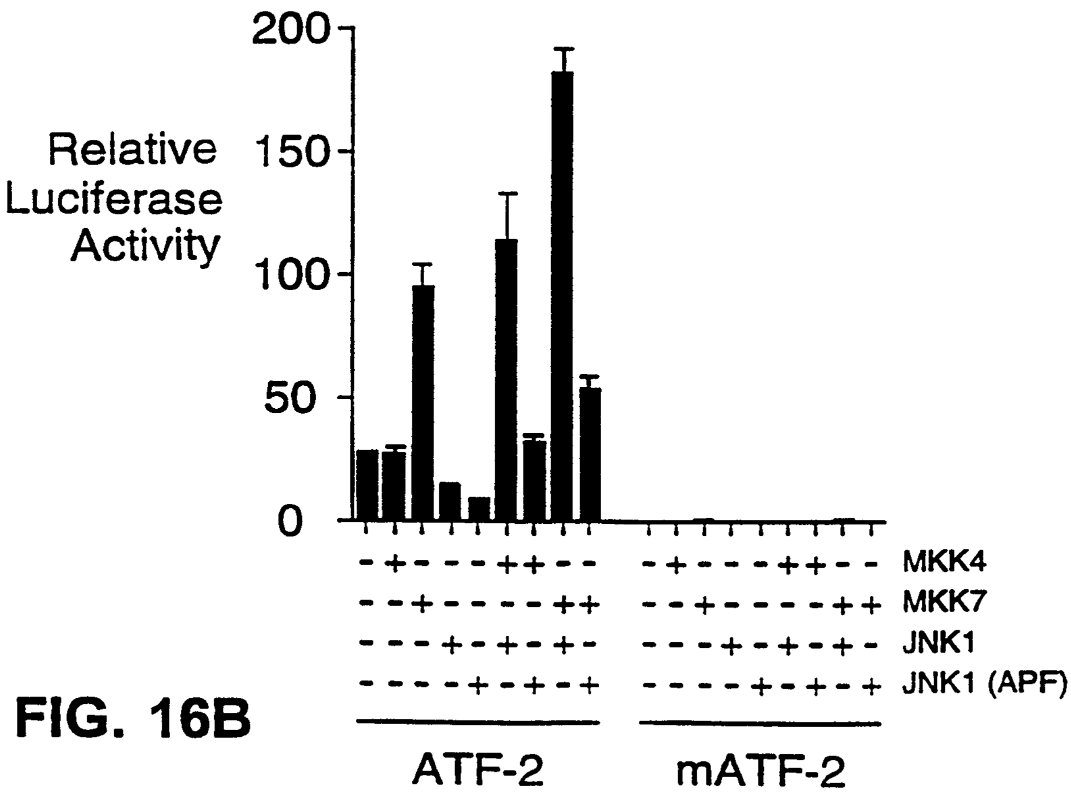

FIG. 16B

SEQUENCE LISTING

(1) GENERAL INFORMATION

(i) APPLICANT: University of Massachusetts

(ii) TITLE OF THE INVENTION: CYTOKINE-, STRESS-, AND ONCOPROTEIN-ACTIVATED HUMAN PROTEIN KINASE KINASES

(iii) NUMBER OF SEQUENCES: 34

(iv) CORRESPONDENCE ADDRESS:
(A) ADDRESSEE: Fish & Richardson P.C.
(B) STREET: 225 Franklin Street
(C) CITY: Boston
(D) STATE: MA
(E) COUNTRY: USA
(F) ZIP: 02110-2804

(v) COMPUTER READABLE FORM:
(A) MEDIUM TYPE: Diskette
(B) COMPUTER: IBM Compatible
(C) OPERATING SYSTEM: Windows95
(D) SOFTWARE: FastSEQ for Windows Version 2.0

(vi) CURRENT APPLICATION DATA:
(A) APPLICATION NUMBER: PCT/US98/14101
(B) FILING DATE: 07-JUL-1998

(vii) PRIOR APPLICATION DATA:
(A) APPLICATION NUMBER: 08/888,429
(B) FILING DATE: 07-JUL-1997

(viii) ATTORNEY/AGENT INFORMATION:
(A) NAME: Fasse, Peter J.
(B) REGISTRATION NUMBER: 32,983
(C) REFERENCE/DOCKET NUMBER: 07917/053WO1

(ix) TELECOMMUNICATION INFORMATION:
(A) TELEPHONE: 617/542-5070
(B) TELEFAX: 617/542-8906
(C) TELEX: 299354

(2) INFORMATION FOR SEQ ID NO:1:

(i) SEQUENCE CHARACTERISTICS:
(A) LENGTH: 2030 base pairs
(B) TYPE: nucleic acid
(C) STRANDEDNESS: double
(D) TOPOLOGY: linear

(ii) MOLECULE TYPE: cDNA

(ix) FEATURE:
(A) NAME/KEY: Coding Sequence
(B) LOCATION: 338...1291

(xi) SEQUENCE DESCRIPTION: SEQ ID NO:1:

```
TGGCTGGCAA TGGCCTTGCT GACCTCGAGC CGGGCCCACG TGGGGACCTT TGGAGCACAG    60
CCTACGATCC TGGTGCAAGG CCGGTGGATG CAGAGGCCAG TCCATATACC ACCCAGGCCT   120
GCGAGGAGCG TGGTCCCCAC CCATCCAGCC CATATGTGCA AGTGCCCTTG ACAGAGAGGC   180
TGGTCATATC CATGGTGACC ATTTATGGGC CACAACAGGT CCCCATCTGC GCAGTGAACC   240
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CTGTGCTGAG CACCTTGCAG ACGTGATCTT GCTTCGTCCT GCAGCACTGT GCGGGGCAGG    300
AAAATCCAAG AGGAAGAAGG ATCTACGGAT ATCCTGC ATG TCC AAG CCA CCC GCA     355
                                         Met Ser Lys Pro Pro Ala
                                          1               5

CCC AAC CCC ACA CCC CCC CGG AAC CTG GAC TCC CGG ACC TTC ATC ACC      403
Pro Asn Pro Thr Pro Pro Arg Asn Leu Asp Ser Arg Thr Phe Ile Thr
            10                  15                  20

ATT GGA GAC AGA AAC TTT GAG GTG GAG GCT GAT GAC TTG GTG ACC ATC      451
Ile Gly Asp Arg Asn Phe Glu Val Glu Ala Asp Asp Leu Val Thr Ile
        25                  30                  35

TCA GAA CTG GGC CGT GGA GCC TAT GGG GTG GTA GAG AAG GTG CGG CAC      499
Ser Glu Leu Gly Arg Gly Ala Tyr Gly Val Val Glu Lys Val Arg His
    40                  45                  50

GCC CAG AGC GGC ACC ATC ATG GCC GTG AAG CGG ATC CGG GCC ACC GTG      547
Ala Gln Ser Gly Thr Ile Met Ala Val Lys Arg Ile Arg Ala Thr Val
55                  60                  65                  70

AAC TCA CAG GAG CAG AAG CGG CTG CTC ATG GAC CTG GAC ATC AAC ATG      595
Asn Ser Gln Glu Gln Lys Arg Leu Leu Met Asp Leu Asp Ile Asn Met
                75                  80                  85

CGC ACG GTC GAC TGT TTC TAC ACT GTC ACC TTC TAC GGG GCA CTA TTC      643
Arg Thr Val Asp Cys Phe Tyr Thr Val Thr Phe Tyr Gly Ala Leu Phe
            90                  95                 100

AGA GAG GGA GAC GTG TGG ATC TGC ATG GAG CTC ATG GAC ACA TCC TTG      691
Arg Glu Gly Asp Val Trp Ile Cys Met Glu Leu Met Asp Thr Ser Leu
        105                 110                 115

GAC AAG TTC TAC CGG AAG GTG CTG GAT AAA AAC ATG ACA ATT CCA GAG      739
Asp Lys Phe Tyr Arg Lys Val Leu Asp Lys Asn Met Thr Ile Pro Glu
    120                 125                 130

GAC ATC CTT GGG GAG ATT GCT GTG TCT ATC GTG CGG GCC CTG GAG CAT      787
Asp Ile Leu Gly Glu Ile Ala Val Ser Ile Val Arg Ala Leu Glu His
135                 140                 145                 150

CTG CAC AGC AAG CTG TCG GTG ATC CAC AGA GAT GTG AAG CCC TCC AAT      835
Leu His Ser Lys Leu Ser Val Ile His Arg Asp Val Lys Pro Ser Asn
                155                 160                 165

GTC CTT ATC AAC AAG GAG GGC CAT GTG AAG ATG TGT GAC TTT GGC ATC      883
Val Leu Ile Asn Lys Glu Gly His Val Lys Met Cys Asp Phe Gly Ile
            170                 175                 180

AGT GGC TAC TTG GTG GAC TCT GTG GCC AAG ACG ATG GAT GCC GGC TGC      931
Ser Gly Tyr Leu Val Asp Ser Val Ala Lys Thr Met Asp Ala Gly Cys
        185                 190                 195

AAG CCC TAC ATG GCC CCT GAG AGG ATC AAC CCA GAG CTG AAC CAG AAG      979
Lys Pro Tyr Met Ala Pro Glu Arg Ile Asn Pro Glu Leu Asn Gln Lys
    200                 205                 210

GGC TAC AAT GTC AAG TCC GAC GTC TGG AGC CTG GGC ATC ACC ATG ATT     1027
Gly Tyr Asn Val Lys Ser Asp Val Trp Ser Leu Gly Ile Thr Met Ile
215                 220                 225                 230

GAG ATG GCC ATC CTG CGG TTC CCT TAC GAG TCC TGG GGG ACC CCG TTC     1075
Glu Met Ala Ile Leu Arg Phe Pro Tyr Glu Ser Trp Gly Thr Pro Phe
                235                 240                 245
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```
CAG CAG CTG AAG CAG GTG GTG GAG GAG CCG TCC CCC CAG CTC CCA GCC      1123
Gln Gln Leu Lys Gln Val Val Glu Glu Pro Ser Pro Gln Leu Pro Ala
            250                 255                 260

GAC CGT TTC TCC CCC GAG TTT GTG GAC TTC ACT GCT CAG TGC CTG AGG      1171
Asp Arg Phe Ser Pro Glu Phe Val Asp Phe Thr Ala Gln Cys Leu Arg
        265                 270                 275

AAG AAC CCC GCA GAG CGT ATG AGC TAC CTG GAG CTG ATG GAG CAC CCC      1219
Lys Asn Pro Ala Glu Arg Met Ser Tyr Leu Glu Leu Met Glu His Pro
    280                 285                 290

TTC TTC ACC TTG CAC AAA ACC AAG AAG ACG GAC ATT GCT GCC TTC GTG      1267
Phe Phe Thr Leu His Lys Thr Lys Lys Thr Asp Ile Ala Ala Phe Val
295                 300                 305                 310

AAG AAG ATC CTG GGA GAA GAC TCA TAGGGGCTGG GCCTCGGACC CCACTCCGGC     1321
Lys Lys Ile Leu Gly Glu Asp Ser
                315

CCTCCAGAGC CCCACAGCCC CATCTGCGGG GGCAGTGCTC ACCCACACCA TAAGCTACTG    1381
CCATCCTGGC CCAGGGCATC TGGGAGGAAC CGAGGGGGCT GCTCCCACCT GGCTCTGTGG    1441
CGAGCCATTT GTCCCAAGTG CCAAAGAAGC AGACCATTGG GGCTCCCAGC CAGGCCCTTG    1501
TCGGCCCCAC CAGTGCCTCT CCCTGCTGCT CCTAGGACCC GTCTCCAGCT GCTGAGATCC    1561
TGGACTGAGG GGGCCTGGAT GCCCCCTGTG GATGCTGCTG CCCCTGCACA GCAGGCTGCC    1621
AGTGCCTGGG TGGATGGGCC ACCGCCTTGC CCAGCCTGGA TGCCATCCAA GTTGTATATT    1681
TTTTTAATCT CTCGACTGAA TGGACTTTGC ACACTTTGGC CCAGGGTGGC CACACCTCTA    1741
TCCCGGCTTT GGTGCGGGGT ACACAAGAGG GGATGAGTTG TGTGAATACC CCAAGACTCC    1801
CATGAGGGAG ATGCCATGAG CCGCCCAAGG CCTTCCCCTG GCACTGGCAA ACAGGGCCTC    1861
TGCGGAGCAC ACTGGCTCAC CCAGTCCTGC CCGCCACCGT TATCGGTGTC ATTCACCTTT    1921
CGTGTTTTTT TTAATTTATC CTCTGTTGAT TTTTTCTTTT GCTTTATGGG TTTGGCTTGT    1981
TTTTCTTGCA TGGTTTGGAG CTGATCGCTT CTCCCCCACC CCCTAGGGG                2030
```

(2) INFORMATION FOR SEQ ID NO:2:

(i) SEQUENCE CHARACTERISTICS:
(A) LENGTH: 318 amino acids
(B) TYPE: amino acid
(D) TOPOLOGY: linear

(ii) MOLECULE TYPE: protein

(v) FRAGMENT TYPE: internal

(xi) SEQUENCE DESCRIPTION: SEQ ID NO:2:

```
Met Ser Lys Pro Pro Ala Pro Asn Pro Thr Pro Pro Arg Asn Leu Asp
 1               5                  10                  15
Ser Arg Thr Phe Ile Thr Ile Gly Asp Arg Asn Phe Glu Val Glu Ala
            20                  25                  30
Asp Asp Leu Val Thr Ile Ser Glu Leu Gly Arg Gly Ala Tyr Gly Val
        35                  40                  45
Val Glu Lys Val Arg His Ala Gln Ser Gly Thr Ile Met Ala Val Lys
    50                  55                  60
Arg Ile Arg Ala Thr Val Asn Ser Gln Glu Gln Lys Arg Leu Leu Met
65                  70                  75                  80
Asp Leu Asp Ile Asn Met Arg Thr Val Asp Cys Phe Tyr Thr Val Thr
                85                  90                  95
Phe Tyr Gly Ala Leu Phe Arg Glu Gly Asp Val Trp Ile Cys Met Glu
            100                 105                 110
Leu Met Asp Thr Ser Leu Asp Lys Phe Tyr Arg Lys Val Leu Asp Lys
        115                 120                 125
Asn Met Thr Ile Pro Glu Asp Ile Leu Gly Glu Ile Ala Val Ser Ile
    130                 135                 140
```

```
Val Arg Ala Leu Glu His Leu His Ser Lys Leu Ser Val Ile His Arg
145                 150                 155                 160
Asp Val Lys Pro Ser Asn Val Leu Ile Asn Lys Glu Gly His Val Lys
                165                 170                 175
Met Cys Asp Phe Gly Ile Ser Gly Tyr Leu Val Asp Ser Val Ala Lys
            180                 185                 190
Thr Met Asp Ala Gly Cys Lys Pro Tyr Met Ala Pro Glu Arg Ile Asn
        195                 200                 205
Pro Glu Leu Asn Gln Lys Gly Tyr Asn Val Lys Ser Asp Val Trp Ser
    210                 215                 220
Leu Gly Ile Thr Met Ile Glu Met Ala Ile Leu Arg Phe Pro Tyr Glu
225                 230                 235                 240
Ser Trp Gly Thr Pro Phe Gln Gln Leu Lys Gln Val Val Glu Glu Pro
                245                 250                 255
Ser Pro Gln Leu Pro Ala Asp Arg Phe Ser Pro Glu Phe Val Asp Phe
            260                 265                 270
Thr Ala Gln Cys Leu Arg Lys Asn Pro Ala Glu Arg Met Ser Tyr Leu
        275                 280                 285
Glu Leu Met Glu His Pro Phe Phe Thr Leu His Lys Thr Lys Lys Thr
    290                 295                 300
Asp Ile Ala Ala Phe Val Lys Lys Ile Leu Gly Glu Asp Ser
305                 310                 315
```

(2) INFORMATION FOR SEQ ID NO:3:

(i) SEQUENCE CHARACTERISTICS:
(A) LENGTH: 1602 base pairs
(B) TYPE: nucleic acid
(C) STRANDEDNESS: double
(D) TOPOLOGY: linear

(ii) MOLECULE TYPE: cDNA

(ix) FEATURE:
(A) NAME/KEY: Coding Sequence
(B) LOCATION: 244...1245

(xi) SEQUENCE DESCRIPTION: SEQ ID NO:3:

```
TAGCTGCAGC ACAGCCTTCC CTAACGTTGC AACTGGGGGA AAAATCACTT TCCAGTCTGT      60
TTTGCAAGGT GTGCATTTCC ATCTTGATTC CCTGAAAGTC CATCTGCTGC ATCGGTCAAG     120
AGAAACTCCA CTTGCATGAA GATTGCACGC CTGCAGCTTG CATCTTTGTT GCAAAACTAG     180
CTACAGAAGA GAAGCAAGGC AAAGTCTTTT GTGCTCCCCT CCCCCATCAA AGGAAAGGGG     240
AAA ATG TCT CAG TCG AAA GGC AAG AAG CGA AAC CCT GGC CTT AAA ATT       288
    Met Ser Gln Ser Lys Gly Lys Lys Arg Asn Pro Gly Leu Lys Ile
      1               5                  10                  15

CCA AAA GAA GCA TTT GAA CAA CCT CAG ACC AGT TCC ACA CCA CCT AGA       336
Pro Lys Glu Ala Phe Glu Gln Pro Gln Thr Ser Ser Thr Pro Pro Arg
                 20                  25                  30

GAT TTA GAC TCC AAG GCT TGC ATT TCT ATT GGA AAT CAG AAC TTT GAG       384
Asp Leu Asp Ser Lys Ala Cys Ile Ser Ile Gly Asn Gln Asn Phe Glu
             35                  40                  45

GTG AAG GCA GAT GAC CTG GAG CCT ATA ATG GAA CTG GGA CGA GGT GCG       432
Val Lys Ala Asp Asp Leu Glu Pro Ile Met Glu Leu Gly Arg Gly Ala
         50                  55                  60

TAC GGG GTG GTG GAG AAG ATG CGG CAC GTG CCC AGC GGG CAG ATC ATG       480
Tyr Gly Val Val Glu Lys Met Arg His Val Pro Ser Gly Gln Ile Met
     65                  70                  75
```

```
GCA GTG AAG CGG ATC CGA GCC ACA GTA AAT AGC CAG GAA CAG AAA CGG      528
Ala Val Lys Arg Ile Arg Ala Thr Val Asn Ser Gln Glu Gln Lys Arg
 80                  85                  90                  95

CTA CTG ATG GAT TTG GAT ATT TCC ATG AGG ACG GTG GAC TGT CCA TTC      576
Leu Leu Met Asp Leu Asp Ile Ser Met Arg Thr Val Asp Cys Pro Phe
            100                 105                 110

ACT GTC ACC TTT TAT GGC GCA CTG TTT CGG GAG GGT GAT GTG TGG ATC      624
Thr Val Thr Phe Tyr Gly Ala Leu Phe Arg Glu Gly Asp Val Trp Ile
        115                 120                 125

TGC ATG GAG CTC ATG GAT ACA TCA CTA GAT AAA TTC TAC AAA CAA GTT      672
Cys Met Glu Leu Met Asp Thr Ser Leu Asp Lys Phe Tyr Lys Gln Val
    130                 135                 140

ATT GAT AAA GGC CAG ACA ATT CCA GAG GAC ATC TTA GGG AAA ATA GCA      720
Ile Asp Lys Gly Gln Thr Ile Pro Glu Asp Ile Leu Gly Lys Ile Ala
    145                 150                 155

GTT TCT ATT GTA AAA GCA TTA GAA CAT TTA CAT AGT AAG CTG TCT GTC      768
Val Ser Ile Val Lys Ala Leu Glu His Leu His Ser Lys Leu Ser Val
160                 165                 170                 175

ATT CAC AGA GAC GTC AAG CCT TCT AAT GTA CTC ATC AAT GCT CTC GGT      816
Ile His Arg Asp Val Lys Pro Ser Asn Val Leu Ile Asn Ala Leu Gly
            180                 185                 190

CAA GTG AAG ATG TGC GAT TTT GGA ATC AGT GGC TAC TTG GTG GAC TCT      864
Gln Val Lys Met Cys Asp Phe Gly Ile Ser Gly Tyr Leu Val Asp Ser
            195                 200                 205

GTT GCT AAA ACA ATT GAT GCA GGT TGC AAA CCA TAC ATG GCC CCT GAA      912
Val Ala Lys Thr Ile Asp Ala Gly Cys Lys Pro Tyr Met Ala Pro Glu
    210                 215                 220

AGA ATA AAC CCA GAG CTC AAC CAG AAG GGA TAC AGT GTG AAG TCT GAC      960
Arg Ile Asn Pro Glu Leu Asn Gln Lys Gly Tyr Ser Val Lys Ser Asp
    225                 230                 235

ATT TGG AGT CTG GGC ATC ACG ATG ATT GAG TTG GCC ATC CTT CGA TTT     1008
Ile Trp Ser Leu Gly Ile Thr Met Ile Glu Leu Ala Ile Leu Arg Phe
240                 245                 250                 255

CCC TAT GAT TCA TGG GGA ACT CCA TTT CAG CAG CTC AAA CAG GTG GTA     1056
Pro Tyr Asp Ser Trp Gly Thr Pro Phe Gln Gln Leu Lys Gln Val Val
            260                 265                 270

GAG GAG CCA TCG CCA CAA CTC CCA GCA GAC AAG TTC TCT GCA GAG TTT     1104
Glu Glu Pro Ser Pro Gln Leu Pro Ala Asp Lys Phe Ser Ala Glu Phe
        275                 280                 285

GTT GAC TTT ACC TCA CAG TGC TTA AAG AAG AAT TCC AAA GAA CGG CCT     1152
Val Asp Phe Thr Ser Gln Cys Leu Lys Lys Asn Ser Lys Glu Arg Pro
        290                 295                 300

ACA TAC CCA GAG CTA ATG CAA CAT CCA TTT TTC ACC CTA CAT GAA TCC     1200
Thr Tyr Pro Glu Leu Met Gln His Pro Phe Phe Thr Leu His Glu Ser
    305                 310                 315

AAA GGA ACA GAT GTG GCA TCT TTT GTA AAA CTG ATT CTT GGA GAC TAAAA   1250
Lys Gly Thr Asp Val Ala Ser Phe Val Lys Leu Ile Leu Gly Asp
320                 325                 330

AGCAGTGGAC TTAATCGGTT GACCCTACTG TGGATTGGTG GGTTTCGGGG TGAAGCAAGT   1310
TCACTACAGC ATCAATAGAA AGTCATCTTT GAGATAATTT AACCCTGCCT CTCAGAGGGT   1370
TTTCTCTCCC AATTTTCTTT TTACTCCCCC TCTTAAGGGG GCCTTGGAAT CTATAGTATA   1430
```

```
GAATGAACTG TCTAGATGGA TGAATTATGA TAAAGGCTTA GGACTTCAAA AGGTGATTAA   1490
ATATTTAATG ATGTGTCATA TGAGTCCTCA AAAAAAAAAA AAAAAAAAAA AAAAAAAAAA   1550
AAAAAAAAAA AAAAAAAAAA AAAAAAAAAA AAAAAAAAAA AAAAAAAAAA AA           1602
```

(2) INFORMATION FOR SEQ ID NO:4:

(i) SEQUENCE CHARACTERISTICS:
(A) LENGTH: 334 amino acids
(B) TYPE: amino acid
(D) TOPOLOGY: linear

(ii) MOLECULE TYPE: protein

(v) FRAGMENT TYPE: internal

(xi) SEQUENCE DESCRIPTION: SEQ ID NO:4:

```
Met Ser Gln Ser Lys Gly Lys Lys Arg Asn Pro Gly Leu Lys Ile Pro
 1               5                  10                  15
Lys Glu Ala Phe Glu Gln Pro Gln Thr Ser Ser Thr Pro Pro Arg Asp
            20                  25                  30
Leu Asp Ser Lys Ala Cys Ile Ser Ile Gly Asn Gln Asn Phe Glu Val
        35                  40                  45
Lys Ala Asp Asp Leu Glu Pro Ile Met Glu Leu Gly Arg Gly Ala Tyr
    50                  55                  60
Gly Val Val Glu Lys Met Arg His Val Pro Ser Gly Gln Ile Met Ala
65                  70                  75                  80
Val Lys Arg Ile Arg Ala Thr Val Asn Ser Gln Glu Gln Lys Arg Leu
                85                  90                  95
Leu Met Asp Leu Asp Ile Ser Met Arg Thr Val Asp Cys Pro Phe Thr
            100                 105                 110
Val Thr Phe Tyr Gly Ala Leu Phe Arg Glu Gly Asp Val Trp Ile Cys
        115                 120                 125
Met Glu Leu Met Asp Thr Ser Leu Asp Lys Phe Tyr Lys Gln Val Ile
    130                 135                 140
Asp Lys Gly Gln Thr Ile Pro Glu Asp Ile Leu Gly Lys Ile Ala Val
145                 150                 155                 160
Ser Ile Val Lys Ala Leu Glu His Leu His Ser Lys Leu Ser Val Ile
                165                 170                 175
His Arg Asp Val Lys Pro Ser Asn Val Leu Ile Asn Ala Leu Gly Gln
            180                 185                 190
Val Lys Met Cys Asp Phe Gly Ile Ser Gly Tyr Leu Val Asp Ser Val
        195                 200                 205
Ala Lys Thr Ile Asp Ala Gly Cys Lys Pro Tyr Met Ala Pro Glu Arg
    210                 215                 220
Ile Asn Pro Glu Leu Asn Gln Lys Gly Tyr Ser Val Lys Ser Asp Ile
225                 230                 235                 240
Trp Ser Leu Gly Ile Thr Met Ile Glu Leu Ala Ile Leu Arg Phe Pro
                245                 250                 255
Tyr Asp Ser Trp Gly Thr Pro Phe Gln Gln Leu Lys Gln Val Val Glu
            260                 265                 270
Glu Pro Ser Pro Gln Leu Pro Ala Asp Lys Phe Ser Ala Glu Phe Val
        275                 280                 285
Asp Phe Thr Ser Gln Cys Leu Lys Lys Asn Ser Lys Glu Arg Pro Thr
    290                 295                 300
Tyr Pro Glu Leu Met Gln His Pro Phe Phe Thr Leu His Glu Ser Lys
305                 310                 315                 320
Gly Thr Asp Val Ala Ser Phe Val Lys Leu Ile Leu Gly Asp
                325                 330
```

(2) INFORMATION FOR SEQ ID NO:5:

(i) SEQUENCE CHARACTERISTICS:
(A) LENGTH: 3498 base pairs

(B) TYPE: nucleic acid
(C) STRANDEDNESS: double
(D) TOPOLOGY: linear

(ii) MOLECULE TYPE: cDNA

(ix) FEATURE:
(A) NAME/KEY: Coding Sequence

(B) LOCATION: 40...1128

(xi) SEQUENCE DESCRIPTION: SEQ ID NO:5:

```
CTAGGGTCCC CGGCGCCAGG CCACCCGGCC GTCAGCAGC ATG CAG GGT AAA CGC      54
                                           Met Gln Gly Lys Arg
                                            1               5

AAA GCA CTG AAG TTG AAT TTT GCA AAT CCA CCT TTC AAA TCT ACA GCA    102
Lys Ala Leu Lys Leu Asn Phe Ala Asn Pro Pro Phe Lys Ser Thr Ala
                 10                  15                  20

AGG TTT ACT CTG AAT CCC AAT CCT ACA GGA GTT CAA AAC CCA CAC ATA    150
Arg Phe Thr Leu Asn Pro Asn Pro Thr Gly Val Gln Asn Pro His Ile
             25                  30                  35

GAG AGA CTG AGA ACA CAC AGC ATT GAG TCA TCA GGA AAA CTG AAG ATC    198
Glu Arg Leu Arg Thr His Ser Ile Glu Ser Ser Gly Lys Leu Lys Ile
         40                  45                  50

TCC CCT GAA CAA CAC TGG GAT TTC ACT GCA GAG GAC TTG AAA GAC CTT    246
Ser Pro Glu Gln His Trp Asp Phe Thr Ala Glu Asp Leu Lys Asp Leu
     55                  60                  65

GGA GAA ATT GGA CGA GGA GCT TAT GGT TCT GTC AAC AAA ATG GTC CAC    294
Gly Glu Ile Gly Arg Gly Ala Tyr Gly Ser Val Asn Lys Met Val His
 70                  75                  80                  85

AAA CCA AGT GGG CAA ATA ATG GCA GTT AAA AGA ATT CGG TCA ACA GTG    342
Lys Pro Ser Gly Gln Ile Met Ala Val Lys Arg Ile Arg Ser Thr Val
                 90                  95                 100

GAT GAA AAA GAA CAA AAA CAA CTT CTT ATG GAT TTG GAT GTA GTA ATG    390
Asp Glu Lys Glu Gln Lys Gln Leu Leu Met Asp Leu Asp Val Val Met
            105                 110                 115

CGG AGT AGT GAT TGC CCA TAC ATT GTT CAG TTT TAT GGT GCA CTC TTC    438
Arg Ser Ser Asp Cys Pro Tyr Ile Val Gln Phe Tyr Gly Ala Leu Phe
        120                 125                 130

AGA GAG GGT GAC TGT TGG ATC TGT ATG GAA CTC ATG TCT ACC TCG TTT    486
Arg Glu Gly Asp Cys Trp Ile Cys Met Glu Leu Met Ser Thr Ser Phe
    135                 140                 145

GAT AAG TTT TAC AAA TAT GTA TAT AGT GTA TTA GAT GAT GTT ATT CCA    534
Asp Lys Phe Tyr Lys Tyr Val Tyr Ser Val Leu Asp Asp Val Ile Pro
150                 155                 160                 165

GAA GAA ATT TTA GGC AAA ATC ACT TTA GCA ACT GTG AAA GCA CTA AAC    582
Glu Glu Ile Leu Gly Lys Ile Thr Leu Ala Thr Val Lys Ala Leu Asn
                170                 175                 180

CAC TTA AAA GAA AAC TTG AAA ATT ATT CAC AGA GAT ATC AAA CCT TCC    630
His Leu Lys Glu Asn Leu Lys Ile Ile His Arg Asp Ile Lys Pro Ser
            185                 190                 195
```

```
AAT ATT CTT CTG GAC AGA AGT GGA AAT ATT AAG CTC TGT GAC TTC GGC     678
Asn Ile Leu Leu Asp Arg Ser Gly Asn Ile Lys Leu Cys Asp Phe Gly
        200                 205                 210

ATC AGT GGA CAG CTT GTG GAC TCT ATT GCC AAG ACA AGA GAT GCT GGC     726
Ile Ser Gly Gln Leu Val Asp Ser Ile Ala Lys Thr Arg Asp Ala Gly
    215                 220                 225

TGT AGG CCA TAC ATG GCA CCT GAA AGA ATA GAC CCA AGC GCA TCA CGA     774
Cys Arg Pro Tyr Met Ala Pro Glu Arg Ile Asp Pro Ser Ala Ser Arg
230                 235                 240                 245

CAA GGA TAT GAT GTC CGC TCT GAT GTC TGG AGT TTG GGG ATC ACA TTG     822
Gln Gly Tyr Asp Val Arg Ser Asp Val Trp Ser Leu Gly Ile Thr Leu
                250                 255                 260

TAT GAG TTG GCC ACA GGC CGA TTT CCT TAT CCA AAG TGG AAT AGT GTA     870
Tyr Glu Leu Ala Thr Gly Arg Phe Pro Tyr Pro Lys Trp Asn Ser Val
            265                 270                 275

TTT GAT CAA CTA ACA CAA GTC GTG AAA GGA GAT CCT CCG CAG CTG AGT     918
Phe Asp Gln Leu Thr Gln Val Val Lys Gly Asp Pro Pro Gln Leu Ser
        280                 285                 290

AAT TCT GAG GAA AGG GAA TTC TCC CCG AGT TTC ATC AAC TTT GTC AAC     966
Asn Ser Glu Glu Arg Glu Phe Ser Pro Ser Phe Ile Asn Phe Val Asn
    295                 300                 305

TTG TGC CTT ACG AAG GAT GAA TCC AAA AGG CCA AAG TAT AAA GAG CTT    1014
Leu Cys Leu Thr Lys Asp Glu Ser Lys Arg Pro Lys Tyr Lys Glu Leu
310                 315                 320                 325

CTG AAA CAT CCC TTT ATT TTG ATG TAT GAA GAA CGT GCC GTT GAG GTC    1062
Leu Lys His Pro Phe Ile Leu Met Tyr Glu Glu Arg Ala Val Glu Val
                330                 335                 340

GCA TGC TAT GTT TGT AAA ATC CTG GAT CAA ATG CCA GCT ACT CCC AGC    1110
Ala Cys Tyr Val Cys Lys Ile Leu Asp Gln Met Pro Ala Thr Pro Ser
            345                 350                 355

TCT CCC ATG TAT GTC GAT TGATATCGYT GCTACATCAG ACTCTAGAAA AAAGGGCT    1166
Ser Pro Met Tyr Val Asp
        360

GAGAGGAAGC AAGACGTAAA GAATTTTCAT CCCGTATCAC AGTGTTTTTA TTGCTCGCCC    1226
AGACACCATG TGCAATAAGA TTGGTGTTCG TTTCCATCAT GTCTGTATAC TCCTGTCACC    1286
TAGAACGTGC ATCCTTGTAA TACCTGATTG ATCACACAGT GTTAGTGCTG GTCAGAGAGA    1346
CCTCATCCTG CTCTTTTGTG ATGAACATAT TCATGAAATG TGGAAGTCAG TACGATCAAG    1406
TTGTTGACTG TGATTAGATC ACATCTTAAA TTCATTTCTA GACTCAAAAC CTGGAGATGC    1466
AGCTACTGGA ATGGTGTTTT GTCAGACTTC CAAATCCTGG AAGGACACAG TGATGAATGT    1526
ACTATATCTG AACATAGAAA CTCGGGCTTG AGTGAGAAGA GCTTGCACAG CCAACGAGAC    1586
ACATTGCCTT CTGGAGCTGG GAGACAAAGG AGGAATTTAC TTTCTTCACC AAGTGCAATA    1646
GATTACTGAT GTGATATTCT GTTGCTTTAC AGTTACAGTT GATGTTTGGG GATCGATGTG    1706
CTCAGCCAAA TTTCCTGTTT GAAATATCAT GTTAAATTAG AATGAATTTA TCTTTACCAA    1766
AAACCATGTT GCGTTCAAAG AGGTGAACAT TAAAATATAG AGACAGGACA GAATGTGTTC    1826
TTTTCTCCTC TACCAGTCCT ATTTTTCAAT GGGAAGACTC AGGAGTCTGC CACTTGTCAA    1886
AGAAGGTGCT GATCCTAAGA ATTTTTCATT CTCAGAATTC GGTGTGCTGC CAACTTGATG    1946
TTCCACCTGC CACAAACCAC CAGGACTGAA AGAAGAAAAC AGTACAGAAG GCAAAGTTTA    2006
CAGATGTTTT TAATTCTAGT ATTTTATCTG GAACAACTTG TAGCAGCTAT ATATTTCCCC    2066
TTGGTCCCAA GCCTGATACT TTAGCCATCA TAACTCACTA ACAGGGAGAA GTAGCTAGTA    2126
GCAATGTGCC TTGATTGATT AGATAAAGAT TTCTAGTAGG CAGCAAAAGA CCAAATCTCA    2186
GTTGTTTGCT TCTTGCCATC ACTGGTCCAG GTCTTCAGTT TCCGAATCTC TTTCCCTTCC    2246
CCTGTGGTCT ATTGTCGCTA TGTGACTTGC GCTTAATCCA ATATTTTGCC TTTTTTCTAT    2306
ATCAAAAAAC CTTTACAGTT AGCAGGGATG TTCCTTACCG AGGATTTTTA ACCCCCAATC    2366
TCTCATAATC GCTAGTGTTT AAAAGGCTAA GAATAGTGGG GCCCAACCGA TGTGGTAGGT    2426
GATAAAGAGG CATCTTTTCT AGAGACACAT TGGACCAGAT GAGGATCCGA AACGGCAGCC    2486
TTTACGTTCA TCACCTGCTA GAACCTCTCG TAGTCCATCA CCATTTCTTG GCATTGGAAT    2546
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TCTACTGGAA AAAAATACAA AAAGCAAAAC AAAACCCTCA GCACTGTTAC AAGAGGCCAT  2606
TTAAGTATCT TGTGCTTCTT CACTTACCCA TTAGCCAGGT TCTCATTAGG TTTTGCTTGG  2666
GCCTCCCTGG CACTGAACCT TAGGCTTTGT ATGACAGTGA AGCAGCACTG TGAGTGGTTC  2726
AAGCACACTG GAATATAAAA CAGTCATGGC CTGAGATGCA GGTGATGCCA TTACAGAACC  2786
AAATCGTGGC ACGTATTGCT GTGTCTCCTC TCAGAGTGAC AGTCATAAAT ACTGTCAAAC  2846
AATAAAGGGA GAATGGTGCT GTTTAAAGTC ACATCCCTGT AAATTGCAGA ATTCAAAAGT  2906
GATTATCTCT TTGATCTACT TGCCTCATTT CCCTATCTTC TCCCCCACGG TATCCTAAAC  2966
TTTAGACTTC CCACTGTTCT GAAAGGAGAC ATTGCTCTAT GTCTGCCTTC GACCACAGCA  3026
AGCCATCATC CTCCATTGCT CCCGGGGACT CAAGAGGAAT CTGTTTCTCT GCTGTCAACT  3086
TCCCATCTGG CTCAGCATAG GGTCACTTTG CCATTATGCA AATGGAGATA AAAGCAATTC  3146
TGGCTGTCCA GGAGCTAATC TGACCGTTCT ATTGTGTGGA TGACCACATA AGAAGGCAAT  3206
TTTAGTGTAT TAATCATAGA TTATTATAAA CTATAAACTT AAGGGCAAGG AGTTTATTAC  3266
AATGTATCTT TATTAAAACA AAAGGGTGTA TAGTGTTCAC AAACTGTGAA AATAGTGTAA  3326
GAACTGTACA TTGTGAGCTC TGGTTATTTT TCTCTTGTAC CATAGAAAAA TGTATAAAAA  3386
TTATCAAAAA GCTAATGTGC AGGGATATTG CCTTATTTGT CTGTAAAAAA TGGAGCTCAG  3446
TAACATAACT GCTTCTTGGA GCTTTGGAAT ATTTTATCCT GTATTCTTGT TT          3498
```

(2) INFORMATION FOR SEQ ID NO:6:

(i) SEQUENCE CHARACTERISTICS:
(A) LENGTH: 363 amino acids
(B) TYPE: amino acid
(D) TOPOLOGY: linear

(ii) MOLECULE TYPE: protein

(v) FRAGMENT TYPE: internal

(xi) SEQUENCE DESCRIPTION: SEQ ID NO:6:

```
Met Gln Gly Lys Arg Lys Ala Leu Lys Leu Asn Phe Ala Asn Pro Pro
1               5                   10                  15
Phe Lys Ser Thr Ala Arg Phe Thr Leu Asn Pro Asn Pro Thr Gly Val
            20                  25                  30
Gln Asn Pro His Ile Glu Arg Leu Arg Thr His Ser Ile Glu Ser Ser
        35                  40                  45
Gly Lys Leu Lys Ile Ser Pro Glu Gln His Trp Asp Phe Thr Ala Glu
    50                  55                  60
Asp Leu Lys Asp Leu Gly Glu Ile Gly Arg Gly Ala Tyr Gly Ser Val
65                  70                  75                  80
Asn Lys Met Val His Lys Pro Ser Gly Gln Ile Met Ala Val Lys Arg
                85                  90                  95
Ile Arg Ser Thr Val Asp Glu Lys Glu Gln Lys Gln Leu Leu Met Asp
            100                 105                 110
Leu Asp Val Val Met Arg Ser Ser Asp Cys Pro Tyr Ile Val Gln Phe
        115                 120                 125
Tyr Gly Ala Leu Phe Arg Glu Gly Asp Cys Trp Ile Cys Met Glu Leu
    130                 135                 140
Met Ser Thr Ser Phe Asp Lys Phe Tyr Lys Tyr Val Tyr Ser Val Leu
145                 150                 155                 160
Asp Asp Val Ile Pro Glu Glu Ile Leu Gly Lys Ile Thr Leu Ala Thr
                165                 170                 175
Val Lys Ala Leu Asn His Leu Lys Glu Asn Leu Lys Ile Ile His Arg
            180                 185                 190
Asp Ile Lys Pro Ser Asn Ile Leu Leu Asp Arg Ser Gly Asn Ile Lys
        195                 200                 205
Leu Cys Asp Phe Gly Ile Ser Gly Gln Leu Val Asp Ser Ile Ala Lys
    210                 215                 220
Thr Arg Asp Ala Gly Cys Arg Pro Tyr Met Ala Pro Glu Arg Ile Asp
225                 230                 235                 240
Pro Ser Ala Ser Arg Gln Gly Tyr Asp Val Arg Ser Asp Val Trp Ser
                245                 250                 255
Leu Gly Ile Thr Leu Tyr Glu Leu Ala Thr Gly Arg Phe Pro Tyr Pro
            260                 265                 270
Lys Trp Asn Ser Val Phe Asp Gln Leu Thr Gln Val Val Lys Gly Asp
        275                 280                 285
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Pro Pro Gln Leu Ser Asn Ser Glu Glu Arg Glu Phe Ser Pro Ser Phe
290 295 300
Ile Asn Phe Val Asn Leu Cys Leu Thr Lys Asp Glu Ser Lys Arg Pro
305 310 315 320
Lys Tyr Lys Glu Leu Leu Lys His Pro Phe Ile Leu Met Tyr Glu Glu
325 330 335
Arg Ala Val Glu Val Ala Cys Tyr Val Cys Lys Ile Leu Asp Gln Met
340 345 350
Pro Ala Thr Pro Ser Ser Pro Met Tyr Val Asp
355 360

(2) INFORMATION FOR SEQ ID NO:7:

(i) SEQUENCE CHARACTERISTICS:
(A) LENGTH: 3554 base pairs
(B) TYPE: nucleic acid
(C) STRANDEDNESS: double
(D) TOPOLOGY: linear

(ii) MOLECULE TYPE: cDNA

(ix) FEATURE:
(A) NAME/KEY: Coding Sequence
(B) LOCATION: 6...1184

(xi) SEQUENCE DESCRIPTION: SEQ ID NO:7:

CAACA ATG GCG GCT CCG AGC CCG AGC GGT GGC GGC GGC AGC GGC ACC CCC 50
Met Ala Ala Pro Ser Pro Ser Gly Gly Gly Gly Ser Gly Thr Pro
1 5 10 15

GGC CCC GTA GGG TCC CCG GCG CCA GGC CAC CCG GCC GTC AGC AGC ATG 98
Gly Pro Val Gly Ser Pro Ala Pro Gly His Pro Ala Val Ser Ser Met
20 25 30

CAG GGT AAA CGC AAA GCA CTG AAG TTG AAT TTT GCA AAT CCA CCT TTC 146
Gln Gly Lys Arg Lys Ala Leu Lys Leu Asn Phe Ala Asn Pro Pro Phe
35 40 45

AAA TCT ACA GCA AGG TTT ACT CTG AAT CCC AAT CCT ACA GGA GTT CAA 194
Lys Ser Thr Ala Arg Phe Thr Leu Asn Pro Asn Pro Thr Gly Val Gln
50 55 60

AAC CCA CAC ATA GAG AGA CTG AGA ACA CAC AGC ATT GAG TCA TCA GGA 242
Asn Pro His Ile Glu Arg Leu Arg Thr His Ser Ile Glu Ser Ser Gly
65 70 75

AAA CTG AAG ATC TCC CCT GAA CAA CAC TGG GAT TTC ACT GCA GAG GAC 290
Lys Leu Lys Ile Ser Pro Glu Gln His Trp Asp Phe Thr Ala Glu Asp
80 85 90 95

TTG AAA GAC CTT GGA GAA ATT GGA CGA GGA GCT TAT GGT TCT GTC AAC 338
Leu Lys Asp Leu Gly Glu Ile Gly Arg Gly Ala Tyr Gly Ser Val Asn
100 105 110

AAA ATG GTC CAC AAA CCA AGT GGG CAA ATA ATG GCA GTT AAA AGA ATT 386
Lys Met Val His Lys Pro Ser Gly Gln Ile Met Ala Val Lys Arg Ile
115 120 125

CGG TCA ACA GTG GAT GAA AAA GAA CAA AAA CAA CTT CTT ATG GAT TTG 434
Arg Ser Thr Val Asp Glu Lys Glu Gln Lys Gln Leu Leu Met Asp Leu
130 135 140

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GAT GTA GTA ATG CGG AGT AGT GAT TGC CCA TAC ATT GTT CAG TTT TAT        482
Asp Val Val Met Arg Ser Ser Asp Cys Pro Tyr Ile Val Gln Phe Tyr
    145                 150                 155

GGT GCA CTC TTC AGA GAG GGT GAC TGT TGG ATC TGT ATG GAA CTC ATG        530
Gly Ala Leu Phe Arg Glu Gly Asp Cys Trp Ile Cys Met Glu Leu Met
160                 165                 170                 175

TCT ACC TCG TTT GAT AAG TTT TAC AAA TAT GTA TAT AGT GTA TTA GAT        578
Ser Thr Ser Phe Asp Lys Phe Tyr Lys Tyr Val Tyr Ser Val Leu Asp
                180                 185                 190

GAT GTT ATT CCA GAA GAA ATT TTA GGC AAA ATC ACT TTA GCA ACT GTG        626
Asp Val Ile Pro Glu Glu Ile Leu Gly Lys Ile Thr Leu Ala Thr Val
            195                 200                 205

AAA GCA CTA AAC CAC TTA AAA GAA AAC TTG AAA ATT ATT CAC AGA GAT        674
Lys Ala Leu Asn His Leu Lys Glu Asn Leu Lys Ile Ile His Arg Asp
        210                 215                 220

ATC AAA CCT TCC AAT ATT CTT CTG GAC AGA AGT GGA AAT ATT AAG CTC        722
Ile Lys Pro Ser Asn Ile Leu Leu Asp Arg Ser Gly Asn Ile Lys Leu
    225                 230                 235

TGT GAC TTC GGC ATC AGT GGA CAG CTT GTG GAC TCT ATT GCC AAG ACA        770
Cys Asp Phe Gly Ile Ser Gly Gln Leu Val Asp Ser Ile Ala Lys Thr
240                 245                 250                 255

AGA GAT GCT GGC TGT AGG CCA TAC ATG GCA CCT GAA AGA ATA GAC CCA        818
Arg Asp Ala Gly Cys Arg Pro Tyr Met Ala Pro Glu Arg Ile Asp Pro
                260                 265                 270

AGC GCA TCA CGA CAA GGA TAT GAT GTC CGC TCT GAT GTC TGG AGT TTG        866
Ser Ala Ser Arg Gln Gly Tyr Asp Val Arg Ser Asp Val Trp Ser Leu
            275                 280                 285

GGG ATC ACA TTG TAT GAG TTG GCC ACA GGC CGA TTT CCT TAT CCA AAG        914
Gly Ile Thr Leu Tyr Glu Leu Ala Thr Gly Arg Phe Pro Tyr Pro Lys
        290                 295                 300

TGG AAT AGT GTA TTT GAT CAA CTA ACA CAA GTC GTG AAA GGA GAT CCT        962
Trp Asn Ser Val Phe Asp Gln Leu Thr Gln Val Val Lys Gly Asp Pro
    305                 310                 315

CCG CAG CTG AGT AAT TCT GAG GAA AGG GAA TTC TCC CCG AGT TTC ATC       1010
Pro Gln Leu Ser Asn Ser Glu Glu Arg Glu Phe Ser Pro Ser Phe Ile
320                 325                 330                 335

AAC TTT GTC AAC TTG TGC CTT ACG AAG GAT GAA TCC AAA AGG CCA AAG       1058
Asn Phe Val Asn Leu Cys Leu Thr Lys Asp Glu Ser Lys Arg Pro Lys
                340                 345                 350

TAT AAA GAG CTT CTG AAA CAT CCC TTT ATT TTG ATG TAT GAA GAA CGT       1106
Tyr Lys Glu Leu Leu Lys His Pro Phe Ile Leu Met Tyr Glu Glu Arg
            355                 360                 365

GCC GTT GAG GTC GCA TGC TAT GTT TGT AAA ATC CTG GAT CAA ATG CCA       1154
Ala Val Glu Val Ala Cys Tyr Val Cys Lys Ile Leu Asp Gln Met Pro
        370                 375                 380

GCT ACT CCC AGC TCT CCC ATG TAT GTC GAT TGATATCGYT GCTACATCAG ACT     1207
Ala Thr Pro Ser Ser Pro Met Tyr Val Asp
    385                 390

CTAGAAAAAA GGGCTGAGAG GAAGCAAGAC GTAAAGAATT TTCATCCCGT ATCACAGTGT     1267
TTTTATTGCT CGCCCAGACA CCATGTGCAA TAAGATTGGT GTTCGTTTCC ATCATGTCTG     1327
TATACTCCTG TCACCTAGAA CGTGCATCCT TGTAATACCT GATTGATCAC ACAGTGTTAG     1387
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TGCTGGTCAG AGAGACCTCA TCCTGCTCTT TTGTGATGAA CATATTCATG AAATGTGGAA   1447
GTCAGTACGA TCAAGTTGTT GACTGTGATT AGATCACATC TTAAATTCAT TTCTAGACTC   1507
AAAACCTGGA GATGCAGCTA CTGGAATGGT GTTTTGTCAG ACTTCCAAAT CCTGGAAGGA   1567
CACAGTGATG AATGTACTAT ATCTGAACAT AGAAACTCGG GCTTGAGTGA GAAGAGCTTG   1627
CACAGCCAAC GAGACACATT GCCTTCTGGA GCTGGGAGAC AAAGGAGGAA TTTACTTTCT   1687
TCACCAAGTG CAATAGATTA CTGATGTGAT ATTCTGTTGC TTTACAGTTA CAGTTGATGT   1747
TTGGGGATCG ATGTGCTCAG CCAAATTTCC TGTTTGAAAT ATCATGTTAA ATTAGAATGA   1807
ATTTATCTTT ACCAAAAACC ATGTTGCGTT CAAAGAGGTG AACATTAAAA TATAGAGACA   1867
GGACAGAATG TGTTCTTTTC TCCTCTACCA GTCCTATTTT TCAATGGGAA GACTCAGGAG   1927
TCTGCCACTT GTCAAAGAAG GTGCTGATCC TAAGAATTTT TCATTCTCAG AATTCGGTGT   1987
GCTGCCAACT TGATGTTCCA CCTGCCACAA ACCACCAGGA CTGAAAGAAG AAAACAGTAC   2047
AGAAGGCAAA GTTTACAGAT GTTTTTAATT CTAGTATTTT ATCTGGAACA ACTTGTAGCA   2107
GCTATATATT TCCCCTTGGT CCCAAGCCTG ATACTTTAGC CATCATAACT CACTAACAGG   2167
GAGAAGTAGC TAGTAGCAAT GTGCCTTGAT TGATTAGATA AAGATTTCTA GTAGGCAGCA   2227
AAAGACCAAA TCTCAGTTGT TTGCTTCTTG CCATCACTGG TCCAGGTCTT CAGTTTCCGA   2287
ATCTCTTTCC CTTCCCCTGT GGTCTATTGT CGCTATGTGA CTTGCGCTTA ATCCAATATT   2347
TTGCCTTTTT TCTATATCAA AAAACCTTTA CAGTTAGCAG GGATGTTCCT TACCGAGGAT   2407
TTTTAACCCC CAATCTCTCA TAATCGCTAG TGTTTAAAAG GCTAAGAATA GTGGGGCCCA   2467
ACCGATGTGG TAGGTGATAA AGAGGCATCT TTTCTAGAGA CACATTGGAC CAGATGAGGA   2527
TCCGAAACGG CAGCCTTTAC GTTCATCACC TGCTAGAACC TCTCGTAGTC CATCACCATT   2587
TCTTGGCATT GGAATTCTAC TGGAAAAAAA TACAAAAAGC AAAACAAAAC CCTCAGCACT   2647
GTTACAAGAG GCCATTTAAG TATCTTGTGC TTCTTCACTT ACCCATTAGC CAGGTTCTCA   2707
TTAGGTTTTG CTTGGGCCTC CCTGGCACTG AACCTTAGGC TTTGTATGAC AGTGAAGCAG   2767
CACTGTGAGT GGTTCAAGCA CACTGGAATA TAAAACAGTC ATGGCCTGAG ATGCAGGTGA   2827
TGCCATTACA GAACCAAATC GTGGCACGTA TTGCTGTGTC TCCTCTCAGA GTGACAGTCA   2887
TAAATACTGT CAAACAATAA AGGGAGAATG GTGCTGTTTA AAGTCACATC CCTGTAAATT   2947
GCAGAATTCA AAAGTGATTA TCTCTTTGAT CTACTTGCCT CATTTCCCTA TCTTCTCCCC   3007
CACGGTATCC TAAACTTTAG ACTTCCCACT GTTCTGAAAG GAGACATTGC TCTATGTCTG   3067
CCTTCGACCA CAGCAAGCCA TCATCCTCCA TTGCTCCCGG GGACTCAAGA GGAATCTGTT   3127
TCTCTGCTGT CAACTTCCCA TCTGGCTCAG CATAGGGTCA CTTTGCCATT ATGCAAATGG   3187
AGATAAAAGC AATTCTGGCT GTCCAGGAGC TAATCTGACC GTTCTATTGT GTGGATGACC   3247
ACATAAGAAG GCAATTTTAG TGTATTAATC ATAGATTATT ATAAACTATA AACTTAAGGG   3307
CAAGGAGTTT ATTACAATGT ATCTTTATTA AAACAAAAGG GTGTATAGTG TTCACAAACT   3367
GTGAAAATAG TGTAAGAACT GTACATTGTG AGCTCTGGTT ATTTTTCTCT TGTACCATAG   3427
AAAAATGTAT AAAAATTATC AAAAAGCTAA TGTGCAGGGA TATTGCCTTA TTTGTCTGTA   3487
AAAAATGGAG CTCAGTAACA TAACTGCTTC TTGGAGCTTT GGAATATTTT ATCCTGTATT   3547
CTTGTTT                                                             3554
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(2) INFORMATION FOR SEQ ID NO:8:

(i) SEQUENCE CHARACTERISTICS:
(A) LENGTH: 393 amino acids
(B) TYPE: amino acid
(D) TOPOLOGY: linear

(ii) MOLECULE TYPE: protein

(v) FRAGMENT TYPE: internal

(xi) SEQUENCE DESCRIPTION: SEQ ID NO:8:

```
Met Ala Ala Pro Ser Pro Ser Gly Gly Gly Gly Ser Gly Thr Pro Gly
  1               5                  10                  15
Pro Val Gly Ser Pro Ala Pro Gly His Pro Ala Val Ser Ser Met Gln
             20                  25                  30
Gly Lys Arg Lys Ala Leu Lys Leu Asn Phe Ala Asn Pro Pro Phe Lys
         35                  40                  45
Ser Thr Ala Arg Phe Thr Leu Asn Pro Asn Pro Thr Gly Val Gln Asn
     50                  55                  60
Pro His Ile Glu Arg Leu Arg Thr His Ser Ile Glu Ser Ser Gly Lys
 65                  70                  75                  80
Leu Lys Ile Ser Pro Glu Gln His Trp Asp Phe Thr Ala Glu Asp Leu
                 85                  90                  95
Lys Asp Leu Gly Glu Ile Gly Arg Gly Ala Tyr Gly Ser Val Asn Lys
            100                 105                 110
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Met Val His Lys Pro Ser Gly Gln Ile Met Ala Val Lys Arg Ile Arg
        115                 120                 125
Ser Thr Val Asp Glu Lys Glu Gln Lys Gln Leu Leu Met Asp Leu Asp
    130                 135                 140
Val Val Met Arg Ser Ser Asp Cys Pro Tyr Ile Val Gln Phe Tyr Gly
145                 150                 155                 160
Ala Leu Phe Arg Glu Gly Asp Cys Trp Ile Cys Met Glu Leu Met Ser
                165                 170                 175
Thr Ser Phe Asp Lys Phe Tyr Lys Tyr Val Tyr Ser Val Leu Asp Asp
            180                 185                 190
Val Ile Pro Glu Glu Ile Leu Gly Lys Ile Thr Leu Ala Thr Val Lys
        195                 200                 205
Ala Leu Asn His Leu Lys Glu Asn Leu Lys Ile Ile His Arg Asp Ile
    210                 215                 220
Lys Pro Ser Asn Ile Leu Leu Asp Arg Ser Gly Asn Ile Lys Leu Cys
225                 230                 235                 240
Asp Phe Gly Ile Ser Gly Gln Leu Val Asp Ser Ile Ala Lys Thr Arg
                245                 250                 255
Asp Ala Gly Cys Arg Pro Tyr Met Ala Pro Glu Arg Ile Asp Pro Ser
            260                 265                 270
Ala Ser Arg Gln Gly Tyr Asp Val Arg Ser Asp Val Trp Ser Leu Gly
        275                 280                 285
Ile Thr Leu Tyr Glu Leu Ala Thr Gly Arg Phe Pro Tyr Pro Lys Trp
    290                 295                 300
Asn Ser Val Phe Asp Gln Leu Thr Gln Val Val Lys Gly Asp Pro Pro
305                 310                 315                 320
Gln Leu Ser Asn Ser Glu Glu Arg Glu Phe Ser Pro Ser Phe Ile Asn
                325                 330                 335
Phe Val Asn Leu Cys Leu Thr Lys Asp Glu Ser Lys Arg Pro Lys Tyr
            340                 345                 350
Lys Glu Leu Leu Lys His Pro Phe Ile Leu Met Tyr Glu Glu Arg Ala
        355                 360                 365
Val Glu Val Ala Cys Tyr Val Cys Lys Ile Leu Asp Gln Met Pro Ala
    370                 375                 380
Thr Pro Ser Ser Pro Met Tyr Val Asp
385                 390
```

(2) INFORMATION FOR SEQ ID NO:9:

(i) SEQUENCE CHARACTERISTICS:
(A) LENGTH: 3576 base pairs
(B) TYPE: nucleic acid
(C) STRANDEDNESS: double
(D) TOPOLOGY: linear

(ii) MOLECULE TYPE: cDNA

(ix) FEATURE:
(A) NAME/KEY: Coding Sequence
(B) LOCATION: 10...1206

(xi) SEQUENCE DESCRIPTION: SEQ ID NO:9:

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CTCCCAACA ATG GCG GCT CCG AGC CCG AGC GGC GGC GGC GGC TCC GGG GGC     51
          Met Ala Ala Pro Ser Pro Ser Gly Gly Gly Gly Ser Gly Gly
            1               5                  10

GGC AGC GGC AGC GGC ACC CCC GGC CCC GTA GGG TCC CCG GCG CCA GGC       99
Gly Ser Gly Ser Gly Thr Pro Gly Pro Val Gly Ser Pro Ala Pro Gly
 15                 20                  25                  30

CAC CCG GCC GTC AGC AGC ATG CAG GGT AAA CGC AAA GCA CTG AAG TTG      147
His Pro Ala Val Ser Ser Met Gln Gly Lys Arg Lys Ala Leu Lys Leu
                35                  40                  45
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AAT TTT GCA AAT CCA CCT TTC AAA TCT ACA GCA AGG TTT ACT CTG AAT    195
Asn Phe Ala Asn Pro Pro Phe Lys Ser Thr Ala Arg Phe Thr Leu Asn
             50                  55                  60

CCC AAT CCT ACA GGA GTT CAA AAC CCA CAC ATA GAG AGA CTG AGA ACA    243
Pro Asn Pro Thr Gly Val Gln Asn Pro His Ile Glu Arg Leu Arg Thr
         65                  70                  75

CAC AGC ATT GAG TCA TCA GGA AAA CTG AAG ATC TCC CCT GAA CAA CAC    291
His Ser Ile Glu Ser Ser Gly Lys Leu Lys Ile Ser Pro Glu Gln His
     80                  85                  90

TGG GAT TTC ACT GCA GAG GAC TTG AAA GAC CTT GGA GAA ATT GGA CGA    339
Trp Asp Phe Thr Ala Glu Asp Leu Lys Asp Leu Gly Glu Ile Gly Arg
 95                 100                 105                 110

GGA GCT TAT GGT TCT GTC AAC AAA ATG GTC CAC AAA CCA AGT GGG CAA    387
Gly Ala Tyr Gly Ser Val Asn Lys Met Val His Lys Pro Ser Gly Gln
                115                 120                 125

ATA ATG GCA GTT AAA AGA ATT CGG TCA ACA GTG GAT GAA AAA GAA CAA    435
Ile Met Ala Val Lys Arg Ile Arg Ser Thr Val Asp Glu Lys Glu Gln
            130                 135                 140

AAA CAA CTT CTT ATG GAT TTG GAT GTA GTA ATG CGG AGT AGT GAT TGC    483
Lys Gln Leu Leu Met Asp Leu Asp Val Val Met Arg Ser Ser Asp Cys
        145                 150                 155

CCA TAC ATT GTT CAG TTT TAT GGT GCA CTC TTC AGA GAG GGT GAC TGT    531
Pro Tyr Ile Val Gln Phe Tyr Gly Ala Leu Phe Arg Glu Gly Asp Cys
    160                 165                 170

TGG ATC TGT ATG GAA CTC ATG TCT ACC TCG TTT GAT AAG TTT TAC AAA    579
Trp Ile Cys Met Glu Leu Met Ser Thr Ser Phe Asp Lys Phe Tyr Lys
175                 180                 185                 190

TAT GTA TAT AGT GTA TTA GAT GAT GTT ATT CCA GAA GAA ATT TTA GGC    627
Tyr Val Tyr Ser Val Leu Asp Asp Val Ile Pro Glu Glu Ile Leu Gly
                195                 200                 205

AAA ATC ACT TTA GCA ACT GTG AAA GCA CTA AAC CAC TTA AAA GAA AAC    675
Lys Ile Thr Leu Ala Thr Val Lys Ala Leu Asn His Leu Lys Glu Asn
            210                 215                 220

TTG AAA ATT ATT CAC AGA GAT ATC AAA CCT TCC AAT ATT CTT CTG GAC    723
Leu Lys Ile Ile His Arg Asp Ile Lys Pro Ser Asn Ile Leu Leu Asp
        225                 230                 235

AGA AGT GGA AAT ATT AAG CTC TGT GAC TTC GGC ATC AGT GGA CAG CTT    771
Arg Ser Gly Asn Ile Lys Leu Cys Asp Phe Gly Ile Ser Gly Gln Leu
    240                 245                 250

GTG GAC TCT ATT GCC AAG ACA AGA GAT GCT GGC TGT AGG CCA TAC ATG    819
Val Asp Ser Ile Ala Lys Thr Arg Asp Ala Gly Cys Arg Pro Tyr Met
255                 260                 265                 270

GCA CCT GAA AGA ATA GAC CCA AGC GCA TCA CGA CAA GGA TAT GAT GTC    867
Ala Pro Glu Arg Ile Asp Pro Ser Ala Ser Arg Gln Gly Tyr Asp Val
                275                 280                 285

CGC TCT GAT GTC TGG AGT TTG GGG ATC ACA TTG TAT GAG TTG GCC ACA    915
Arg Ser Asp Val Trp Ser Leu Gly Ile Thr Leu Tyr Glu Leu Ala Thr
            290                 295                 300

GGC CGA TTT CCT TAT CCA AAG TGG AAT AGT GTA TTT GAT CAA CTA ACA    963
Gly Arg Phe Pro Tyr Pro Lys Trp Asn Ser Val Phe Asp Gln Leu Thr
        305                 310                 315
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CAA GTC GTG AAA GGA GAT CCT CCG CAG CTG AGT AAT TCT GAG GAA AGG      1011
Gln Val Val Lys Gly Asp Pro Pro Gln Leu Ser Asn Ser Glu Glu Arg
    320                 325                 330

GAA TTC TCC CCG AGT TTC ATC AAC TTT GTC AAC TTG TGC CTT ACG AAG      1059
Glu Phe Ser Pro Ser Phe Ile Asn Phe Val Asn Leu Cys Leu Thr Lys
335                 340                 345                 350

GAT GAA TCC AAA AGG CCA AAG TAT AAA GAG CTT CTG AAA CAT CCC TTT      1107
Asp Glu Ser Lys Arg Pro Lys Tyr Lys Glu Leu Leu Lys His Pro Phe
                355                 360                 365

ATT TTG ATG TAT GAA GAA CGT GCC GTT GAG GTC GCA TGC TAT GTT TGT      1155
Ile Leu Met Tyr Glu Glu Arg Ala Val Glu Val Ala Cys Tyr Val Cys
            370                 375                 380

AAA ATC CTG GAT CAA ATG CCA GCT ACT CCC AGC TCT CCC ATG TAT GTC      1203
Lys Ile Leu Asp Gln Met Pro Ala Thr Pro Ser Ser Pro Met Tyr Val
        385                 390                 395

GAT TGATATCGCT GCTACATCAG ACTCTAGAAA AAAGGGCTGA GAGGAAGCAA GACGTA    1262
Asp

AAGAATTTTC ATCCCGTATC ACAGTGTTTT TATTGCTCGC CCAGACACCA TGTGCAATAA    1322
GATTGGTGTT CGTTTCCATC ATGTCTGTAT ACTCCTGTCA CCTAGAACGT GCATCCTTGT    1382
AATACCTGAT TGATCACACA GTGTTAGTGC TGGTCAGAGA GACCTCATCC TGCTCTTTTG    1442
TGATGAACAT ATTCATGAAA TGTGGAAGTC AGTACGATCA AGTTGTTGAC TGTGATTAGA    1502
TCACATCTTA AATTCATTTC TAGACTCAAA ACCTGGAGAT GCAGCTACTG GAATGGTGTT    1562
TTGTCAGACT TCCAAATCCT GGAAGGACAC AGTGATGAAT GTACTATATC TGAACATAGA    1622
AACTCGGGCT TGAGTGAGAA GAGCTTGCAC AGCCAACGAG ACACATTGCC TTCTGGAGCT    1682
GGGAGACAAA GGAGGAATTT ACTTTCTTCA CCAAGTGCAA TAGATTACTG ATGTGATATT    1742
CTGTTGCTTT ACAGTTACAG TTGATGTTTG GGGATCGATG TGCTCAGCCA AATTTCCTGT    1802
TTGAAATATC ATGTTAAATT AGAATGAATT TATCTTTACC AAAAACCATG TTGCGTTCAA    1862
AGAGGTGAAC ATTAAAATAT AGAGACAGGA CAGAATGTGT TCTTTTCTCC TCTACCAGTC    1922
CTATTTTTCA ATGGGAAGAC TCAGGAGTCT GCCACTTGTC AAAGAAGGTG CTGATCCTAA    1982
GAATTTTTCA TTCTCAGAAT TCGGTGTGCT GCCAACTTGA TGTTCCACCT GCCACAAACC    2042
ACCAGGACTG AAAGAAGAAA ACAGTACAGA AGGCAAAGTT TACAGATGTT TTTAATTCTA    2102
GTATTTTATC TGGAACAACT TGTAGCAGCT ATATATTTCC CCTTGGTCCC AAGCCTGATA    2162
CTTTAGCCAT CATAACTCAC TAACAGGGAG AAGTAGCTAG TAGCAATGTG CCTTGATTGA    2222
TTAGATAAAG ATTTCTAGTA GGCAGCAAAA GACCAAATCT CAGTTGTTTG CTTCTTGCCA    2282
TCACTGGTCC AGGTCTTCAG TTTCCGAATC TCTTTCCCTT CCCCTGTGGT CTATTGTCGC    2342
TATGTGACTT GCGCTTAATC CAATATTTTG CCTTTTTTCT ATATCAAAAA ACCTTTACAG    2402
TTAGCAGGGA TGTTCCTTAC CGAGGATTTT TAACCCCCAA TCTCTCATAA TCGCTAGTGT    2462
TTAAAAGGCT AAGAATAGTG GGGCCCAACC GATGTGGTAG GTGATAAAGA GGCATCTTTT    2522
CTAGAGACAC ATTGGACCAG ATGAGGATCC GAAACGGCAG CCTTTACGTT CATCACCTGC    2582
TAGAACCTCT CGTAGTCCAT CACCATTTCT TGGCATTGGA ATTCTACTGG AAAAAAATAC    2642
AAAAAGCAAA ACAAAACCCT CAGCACTGTT ACAAGAGGCC ATTTAAGTAT CTTGTGCTTC    2702
TTCACTTACC CATTAGCCAG GTTCTCATTA GGTTTTGCTT GGGCCTCCCT GGCACTGAAC    2762
CTTAGGCTTT GTATGACAGT GAAGCAGCAC TGTGAGTGGT TCAAGCACAC TGGAATATAA    2822
AACAGTCATG GCCTGAGATG CAGGTGATGC CATTACAGAA CCAAATCGTG GCACGTATTG    2882
CTGTGTCTCC TCTCAGAGTG ACAGTCATAA ATACTGTCAA ACAATAAAGG GAGAATGGTG    2942
CTGTTTAAAG TCACATCCCT GTAAATTGCA GAATTCAAAA GTGATTATCT CTTTGATCTA    3002
CTTGCCTCAT TTCCCTATCT TCTCCCCCAC GGTATCCTAA ACTTTAGACT TCCCACTGTT    3062
CTGAAAGGAG ACATTGCTCT ATGTCTGCCT TCGACCACAG CAAGCCATCA TCCTCCATTG    3122
CTCCCGGGGA CTCAAGAGGA ATCTGTTTCT CTGCTGTCAA CTTCCCATCT GGCTCAGCAT    3182
AGGGTCACTT TGCCATTATG CAAATGGAGA TAAAAGCAAT TCTGGCTGTC CAGGAGCTAA    3242
TCTGACCGTT CTATTGTGTG GATGACCACA TAAGAAGGCA ATTTTAGTGT ATTAATCATA    3302
GATTATTATA AACTATAAAC TTAAGGGCAA GGAGTTTATT ACAATGTATC TTTATTAAAA    3362
CAAAAGGGTG TATAGTGTTC ACAAACTGTG AAAATAGTGT AAGAACTGTA CATTGTGAGC    3422
TCTGGTTATT TTTCTCTTGT ACCATAGAAA AATGTATAAA AATTATCAAA AAGCTAATGT    3482
GCAGGGATAT TGCCTTATTT GTCTGTAAAA AATGGAGCTC AGTAACATAA CTGCTTCTTG    3542
GAGCTTTGGA ATATTTTATC CTGTATTCTT GTTT                                3576
```

(2) INFORMATION FOR SEQ ID NO:10:

(i) SEQUENCE CHARACTERISTICS:
(A) LENGTH: 399 amino acids
(B) TYPE: amino acid
(D) TOPOLOGY: linear

(ii) MOLECULE TYPE: protein

(v) FRAGMENT TYPE: internal

(xi) SEQUENCE DESCRIPTION: SEQ ID NO:10:

```
Met Ala Ala Pro Ser Pro Ser Gly Gly Gly Gly Ser Gly Gly Gly Ser
 1               5                  10                  15
Gly Ser Gly Thr Pro Gly Pro Val Gly Ser Pro Ala Pro Gly His Pro
            20                  25                  30
Ala Val Ser Ser Met Gln Gly Lys Arg Lys Ala Leu Lys Leu Asn Phe
        35                  40                  45
Ala Asn Pro Pro Phe Lys Ser Thr Ala Arg Phe Thr Leu Asn Pro Asn
    50                  55                  60
Pro Thr Gly Val Gln Asn Pro His Ile Glu Arg Leu Arg Thr His Ser
 65                  70                  75                  80
Ile Glu Ser Ser Gly Lys Leu Lys Ile Ser Pro Glu Gln His Trp Asp
                85                  90                  95
Phe Thr Ala Glu Asp Leu Lys Asp Leu Gly Glu Ile Gly Arg Gly Ala
            100                 105                 110
Tyr Gly Ser Val Asn Lys Met Val His Lys Pro Ser Gly Gln Ile Met
        115                 120                 125
Ala Val Lys Arg Ile Arg Ser Thr Val Asp Glu Lys Glu Gln Lys Gln
    130                 135                 140
Leu Leu Met Asp Leu Asp Val Val Met Arg Ser Ser Asp Cys Pro Tyr
145                 150                 155                 160
Ile Val Gln Phe Tyr Gly Ala Leu Phe Arg Glu Gly Asp Cys Trp Ile
                165                 170                 175
Cys Met Glu Leu Met Ser Thr Ser Phe Asp Lys Phe Tyr Lys Tyr Val
            180                 185                 190
Tyr Ser Val Leu Asp Asp Val Ile Pro Glu Glu Ile Leu Gly Lys Ile
        195                 200                 205
Thr Leu Ala Thr Val Lys Ala Leu Asn His Leu Lys Glu Asn Leu Lys
    210                 215                 220
Ile Ile His Arg Asp Ile Lys Pro Ser Asn Ile Leu Leu Asp Arg Ser
225                 230                 235                 240
Gly Asn Ile Lys Leu Cys Asp Phe Gly Ile Ser Gly Gln Leu Val Asp
                245                 250                 255
Ser Ile Ala Lys Thr Arg Asp Ala Gly Cys Arg Pro Tyr Met Ala Pro
            260                 265                 270
Glu Arg Ile Asp Pro Ser Ala Ser Arg Gln Gly Tyr Asp Val Arg Ser
        275                 280                 285
Asp Val Trp Ser Leu Gly Ile Thr Leu Tyr Glu Leu Ala Thr Gly Arg
    290                 295                 300
Phe Pro Tyr Pro Lys Trp Asn Ser Val Phe Asp Gln Leu Thr Gln Val
305                 310                 315                 320
Val Lys Gly Asp Pro Pro Gln Leu Ser Asn Ser Glu Glu Arg Glu Phe
                325                 330                 335
Ser Pro Ser Phe Ile Asn Phe Val Asn Leu Cys Leu Thr Lys Asp Glu
            340                 345                 350
Ser Lys Arg Pro Lys Tyr Lys Glu Leu Leu Lys His Pro Phe Ile Leu
        355                 360                 365
Met Tyr Glu Glu Arg Ala Val Glu Val Ala Cys Tyr Val Cys Lys Ile
    370                 375                 380
Leu Asp Gln Met Pro Ala Thr Pro Ser Ser Pro Met Tyr Val Asp
385                 390                 395
```

(2) INFORMATION FOR SEQ ID NO:11:

(i) SEQUENCE CHARACTERISTICS:
(A) LENGTH: 393 amino acids
(B) TYPE: amino acid
(D) TOPOLOGY: linear

(ii) MOLECULE TYPE: protein

(xi) SEQUENCE DESCRIPTION: SEQ ID NO:11:

```
Met Pro Lys Lys Lys Pro Thr Pro Ile Gln Leu Asn Pro Ala Pro Asp
 1               5                  10                  15
Gly Ser Ala Val Asn Gly Thr Ser Ser Ala Glu Thr Asn Leu Glu Ala
            20                  25                  30
Leu Gln Lys Lys Leu Glu Glu Leu Glu Leu Asp Glu Gln Gln Arg Lys
        35                  40                  45
Arg Leu Glu Ala Phe Leu Thr Gln Lys Gln Lys Val Gly Glu Leu Lys
    50                  55                  60
Asp Asp Asp Phe Glu Lys Ile Ser Glu Leu Gly Ala Gly Asn Gly Gly
65                  70                  75                  80
Val Val Phe Lys Val Ser His Lys Pro Ser Gly Leu Val Met Ala Arg
                85                  90                  95
Lys Leu Ile His Leu Glu Ile Lys Pro Ala Ile Arg Asn Gln Ile Ile
            100                 105                 110
Arg Glu Leu Gln Val Leu His Glu Cys Asn Ser Pro Tyr Ile Val Gly
        115                 120                 125
Phe Tyr Gly Ala Phe Tyr Ser Asp Gly Glu Ile Ser Ile Cys Met Glu
    130                 135                 140
His Met Asp Gly Gly Ser Leu Asp Gln Val Leu Lys Lys Ala Gly Arg
145                 150                 155                 160
Ile Pro Glu Gln Ile Leu Gly Lys Val Ser Ile Ala Val Ile Lys Gly
                165                 170                 175
Leu Thr Tyr Leu Arg Glu Lys His Lys Ile Met His Arg Asp Val Lys
            180                 185                 190
Pro Ser Asn Ile Leu Val Asn Ser Arg Gly Glu Ile Lys Leu Cys Asp
        195                 200                 205
Phe Gly Val Ser Gly Gln Leu Ile Asp Ser Met Ala Asn Ser Phe Val
    210                 215                 220
Gly Thr Arg Ser Tyr Met Ser Pro Glu Arg Leu Gln Gly Thr His Tyr
225                 230                 235                 240
Ser Val Gln Ser Asp Ile Trp Ser Met Gly Leu Ser Leu Val Glu Met
                245                 250                 255
Ala Val Gly Arg Tyr Pro Ile Pro Pro Pro Asp Ala Lys Glu Leu Glu
            260                 265                 270
Leu Met Phe Gly Cys Gln Val Glu Gly Asp Ala Ala Glu Thr Pro Pro
        275                 280                 285
Arg Pro Arg Thr Pro Gly Arg Pro Leu Ser Ser Tyr Gly Met Asp Ser
    290                 295                 300
Arg Pro Pro Met Ala Ile Phe Glu Leu Leu Asp Tyr Ile Val Asn Glu
305                 310                 315                 320
Pro Pro Pro Lys Leu Pro Ser Gly Val Phe Ser Leu Glu Phe Gln Asp
                325                 330                 335
Phe Val Asn Lys Cys Leu Ile Lys Asn Pro Ala Glu Arg Ala Asp Leu
            340                 345                 350
Lys Gln Leu Met Val His Ala Phe Ile Lys Arg Ser Asp Ala Glu Glu
        355                 360                 365
Val Asp Phe Ala Gly Trp Leu Cys Ser Thr Ile Gly Leu Asn Gln Pro
    370                 375                 380
Ser Thr Pro Thr His Ala Ala Gly Val
385                 390
```

(2) INFORMATION FOR SEQ ID NO:12:

(i) SEQUENCE CHARACTERISTICS:
(A) LENGTH: 400 amino acids
(B) TYPE: amino acid
(D) TOPOLOGY: linear

(ii) MOLECULE TYPE: protein

(xi) SEQUENCE DESCRIPTION: SEQ ID NO:12:

```
Met Leu Ala Arg Arg Lys Pro Val Leu Pro Ala Leu Thr Ile Asn Pro
 1               5                  10                  15
Thr Ile Ala Glu Gly Pro Ser Pro Thr Ser Glu Gly Ala Ser Glu Ala
            20                  25                  30
Asn Leu Val Asp Leu Gln Lys Lys Leu Glu Glu Leu Glu Leu Asp Glu
        35                  40                  45
Gln Gln Lys Lys Arg Leu Glu Ala Phe Leu Thr Gln Lys Ala Lys Val
    50                  55                  60
Gly Glu Leu Lys Asp Asp Asp Phe Glu Arg Ile Ser Glu Leu Gly Ala
65                  70                  75                  80
Gly Asn Gly Gly Val Val Thr Lys Val Gln His Arg Pro Ser Gly Leu
                85                  90                  95
Ile Met Ala Arg Lys Leu Ile His Leu Glu Ile Lys Pro Ala Ile Arg
            100                 105                 110
Asn Gln Ile Ile Arg Glu Leu Gln Val Leu His Glu Cys Asn Ser Pro
        115                 120                 125
Tyr Ile Val Gly Phe Tyr Gly Ala Phe Tyr Ser Asp Gly Glu Ile Ser
    130                 135                 140
Ile Cys Met Glu His Met Asp Gly Gly Ser Leu Asp Gln Val Leu Lys
145                 150                 155                 160
Glu Ala Lys Arg Ile Pro Glu Glu Ile Leu Gly Lys Val Ser Ile Ala
                165                 170                 175
Val Leu Arg Gly Leu Ala Tyr Leu Arg Glu Lys His Gln Ile Met His
            180                 185                 190
Arg Asp Val Lys Pro Ser Asn Ile Leu Val Asn Ser Arg Gly Glu Ile
        195                 200                 205
Lys Leu Cys Asp Phe Gly Val Ser Gly Gln Leu Ile Asp Ser Met Ala
    210                 215                 220
Asn Ser Phe Val Gly Thr Arg Ser Tyr Met Ala Pro Glu Arg Leu Gln
225                 230                 235                 240
Gly Thr His Tyr Ser Val Gln Ser Asp Ile Trp Ser Met Gly Leu Ser
                245                 250                 255
Leu Val Glu Leu Ala Val Gly Arg Tyr Pro Ile Pro Pro Pro Asp Ala
            260                 265                 270
Lys Glu Leu Glu Ala Ile Phe Gly Arg Pro Val Val Asp Gly Glu Glu
        275                 280                 285
Gly Glu Pro His Ser Ile Ser Pro Arg Pro Arg Pro Pro Gly Arg Pro
    290                 295                 300
Val Ser Gly His Gly Met Asp Ser Arg Pro Ala Met Ala Ile Phe Glu
305                 310                 315                 320
Leu Leu Asp Tyr Ile Val Asn Glu Pro Pro Pro Lys Leu Pro Asn Gly
                325                 330                 335
Val Phe Thr Pro Asp Phe Gln Glu Phe Val Asn Lys Cys Leu Ile Lys
            340                 345                 350
Asn Pro Ala Glu Arg Ala Asp Leu Lys Met Leu Thr Asn His Thr Phe
        355                 360                 365
Ile Lys Arg Ser Glu Val Glu Glu Val Asp Phe Ala Gly Trp Leu Cys
    370                 375                 380
Lys Thr Leu Arg Leu Asn Gln Pro Gly Thr Pro Thr Arg Thr Ala Val
385                 390                 395                 400
```

(2) INFORMATION FOR SEQ ID NO:13:

(i) SEQUENCE CHARACTERISTICS:
(A) LENGTH: 367 amino acids

(B) TYPE: amino acid
(D) TOPOLOGY: linear

(ii) MOLECULE TYPE: protein

(xi) SEQUENCE DESCRIPTION: SEQ ID NO:13:

```
Gly Thr Thr Pro Arg Thr Gly Asn Ser Asn Asn Ser Asn Ser Gly Ser
 1               5                  10                  15
Ser Gly Gly Gly Gly Leu Phe Ala Asn Phe Ser Lys Tyr Val Asp Ile
            20                  25                  30
Lys Ser Gly Ser Leu Asn Phe Ala Gly Lys Leu Ser Leu Ser Ser Lys
        35                  40                  45
Gly Ile Asp Phe Ser Asn Gly Ser Ser Ser Arg Ile Thr Leu Asp Glu
    50                  55                  60
Leu Glu Phe Leu Asp Glu Leu Gly His Gly Asn Tyr Gly Asn Val Ser
65                  70                  75                  80
Lys Val Leu His Lys Pro Thr Asn Val Ile Met Ala Thr Lys Glu Val
                85                  90                  95
Arg Leu Glu Leu Asp Glu Ala Lys Phe Arg Gln Ile Leu Met Glu Leu
            100                 105                 110
Glu Val Leu His Lys Cys Asn Ser Pro Tyr Ile Val Asp Phe Tyr Gly
        115                 120                 125
Ala Phe Phe Ile Glu Gly Ala Val Tyr Met Cys Met Glu Tyr Met Asp
    130                 135                 140
Gly Gly Ser Leu Asp Lys Ile Tyr Asp Glu Ser Ser Glu Ile Gly Gly
145                 150                 155                 160
Ile Asp Glu Pro Gln Leu Ala Phe Ile Ala Asn Ala Val Ile His Gly
                165                 170                 175
Leu Lys Glu Leu Lys Glu Gln His Asn Ile Ile His Arg Asp Val Lys
            180                 185                 190
Pro Thr Asn Ile Leu Cys Ser Ala Asn Gln Gly Thr Val Lys Leu Cys
        195                 200                 205
Asp Phe Gly Val Ser Gly Asn Leu Val Ala Ser Leu Ala Lys Thr Met
    210                 215                 220
Asn Ile Gly Cys Gln Ser Tyr Met Ala Pro Glu Arg Ile Lys Ser Leu
225                 230                 235                 240
Asn Pro Asp Arg Ala Thr Tyr Thr Val Gln Ser Asp Ile Trp Ser Leu
                245                 250                 255
Gly Leu Ser Ile Leu Glu Met Ala Leu Gly Arg Tyr Pro Tyr Pro Pro
            260                 265                 270
Glu Thr Tyr Asp Asn Ile Phe Ser Gln Leu Ser Ala Ile Val Asp Gly
        275                 280                 285
Pro Pro Pro Arg Leu Pro Ser Asp Lys Phe Ser Ser Asp Ala Gln Asp
    290                 295                 300
Phe Val Ser Leu Cys Leu Gln Lys Ile Pro Glu Arg Arg Pro Thr Tyr
305                 310                 315                 320
Ala Ala Leu Thr Glu His Pro Trp Leu Val Lys Tyr Arg Asn Gln Asp
                325                 330                 335
Val His Met Ser Glu Tyr Ile Thr Glu Arg Leu Glu Arg Arg Asn Lys
            340                 345                 350
Ile Leu Arg Glu Arg Gly Glu Asn Gly Leu Ser Lys Asn Val Pro
        355                 360                 365
```

(2) INFORMATION FOR SEQ ID NO:14:

(i) SEQUENCE CHARACTERISTICS:
(A) LENGTH: 23 base pairs
(B) TYPE: nucleic acid
(C) STRANDEDNESS: single
(D) TOPOLOGY: linear

(ii) MOLECULE TYPE: cDNA

(xi) SEQUENCE DESCRIPTION: SEQ ID NO:14:

TTYTAYGGNG CNTTYTTYAT HGA 23

(2) INFORMATION FOR SEQ ID NO:15:

(i) SEQUENCE CHARACTERISTICS:
(A) LENGTH: 20 base pairs
(B) TYPE: nucleic acid
(C) STRANDEDNESS: single
(D) TOPOLOGY: linear

(ii) MOLECULE TYPE: cDNA

(xi) SEQUENCE DESCRIPTION: SEQ ID NO:15:

```
ATBCTYTCNG GNGCCATKTA                                                   20
```

(2) INFORMATION FOR SEQ ID NO:16:

(i) SEQUENCE CHARACTERISTICS:
(A) LENGTH: 8 amino acids
(B) TYPE: amino acid
(D) TOPOLOGY: linear

(ii) MOLECULE TYPE: peptide

(xi) SEQUENCE DESCRIPTION: SEQ ID NO:16:

```
Asp Tyr Lys Asp Asp Asp Asp Lys
 1               5
```

(2) INFORMATION FOR SEQ ID NO:17:

(i) SEQUENCE CHARACTERISTICS:
(A) LENGTH: 1623 base pairs
(B) TYPE: nucleic acid
(C) STRANDEDNESS: double
(D) TOPOLOGY: linear

(ii) MOLECULE TYPE: cDNA

(ix) FEATURE:
(A) NAME/KEY: Coding Sequence
(B) LOCATION: 281...1318

(xi) SEQUENCE DESCRIPTION: SEQ ID NO:17:

```
GGAAAGGCAG CCTCCTGTAG GTGAAAATTC TGTTCACTAC CTGGCCACCT GGCCTGACTG     60
ACCTTCACAG CTTGATCATC TTCCTGAAGA GGCATTCAGG ATTCCCTCCA TCCCTACCCC    120
TTCTGGACAA AGTCTTCCAC GTTTCCTTCC TGGGAGTTTC TTCCAGGAAC TGGAGATACC    180
CAGAGCCCTG CAACTCCCAC TGGCCAACGA TGGGGGCAGC CGCTCACCAT CCTCAGAGAG    240
CTCCCCACAG CACCCTACAC CCCCCACCCG GCCCCGCCAC  ATG CTG GGG CTC CCA     295
                                             Met Leu Gly Leu Pro
                                              1               5

TCA ACC TTG TTC ACA CCG CGC AGT ATG GAG AGC ATC GAG ATT GAC CAG      343
Ser Thr Leu Phe Thr Pro Arg Ser Met Glu Ser Ile Glu Ile Asp Gln
                 10                  15                  20

AAG CTG CAG GAG ATC ATG AAG CAG ACA GGG TAC CTG ACT ATC GGG GGC      391
Lys Leu Gln Glu Ile Met Lys Gln Thr Gly Tyr Leu Thr Ile Gly Gly
             25                  30                  35

CAG CGT TAT CAG GCA GAA ATC AAT GAC TTG GAG AAC TTG GGT GAG ATG      439
Gln Arg Tyr Gln Ala Glu Ile Asn Asp Leu Glu Asn Leu Gly Glu Met
         40                  45                  50
```

```
GGC AGT GGT ACC TGT GGT CAG GTG TGG AAG ATG CGG TTC CGG AAG ACA      487
Gly Ser Gly Thr Cys Gly Gln Val Trp Lys Met Arg Phe Arg Lys Thr
     55                  60                  65

GGC CAC ATC ATT GCT GTT AAG CAA ATG CGG CGC TCT GGG AAC AAG GAA      535
Gly His Ile Ile Ala Val Lys Gln Met Arg Arg Ser Gly Asn Lys Glu
 70                  75                  80                  85

GAG AAT AAG CGC ATT TTG ATG GAC CTG GAT GTA GTA CTC AAG AGC CAT      583
Glu Asn Lys Arg Ile Leu Met Asp Leu Asp Val Val Leu Lys Ser His
                 90                  95                 100

GAC TGC CCT TAC ATC GTT CAG TGC TTT GGC ACC TTC ATC ACC AAC ACA      631
Asp Cys Pro Tyr Ile Val Gln Cys Phe Gly Thr Phe Ile Thr Asn Thr
            105                 110                 115

GAC GTC TTT ATT GCC ATG GAG CTC ATG GGC ACA TGT GCA GAG AAG CTG      679
Asp Val Phe Ile Ala Met Glu Leu Met Gly Thr Cys Ala Glu Lys Leu
        120                 125                 130

AAG AAA CGA ATG CAG GGC CCC ATT CCA GAG CGA ATC CTG GGC AAC ATG      727
Lys Lys Arg Met Gln Gly Pro Ile Pro Glu Arg Ile Leu Gly Asn Met
    135                 140                 145

ACT GTG GCG ATT GTG AAA GCA CTG TAC TAT CTG AAG GAG AAG CAT GGC      775
Thr Val Ala Ile Val Lys Ala Leu Tyr Tyr Leu Lys Glu Lys His Gly
150                 155                 160                 165

GTC ATC CAT CGC GAT GTC AAA CCC TCC AAC ATC CTG CTA GAT GAG CGG      823
Val Ile His Arg Asp Val Lys Pro Ser Asn Ile Leu Leu Asp Glu Arg
                170                 175                 180

GGC CAG ATC AAG CTC TGT GAC TTT GGC ATC AGT GGC CGC CTT GTT GAC      871
Gly Gln Ile Lys Leu Cys Asp Phe Gly Ile Ser Gly Arg Leu Val Asp
            185                 190                 195

TCC AAA GCC AAA ACA CGG AGT GCT GGC TGT GCT GCC TAT ATG GCT CCC      919
Ser Lys Ala Lys Thr Arg Ser Ala Gly Cys Ala Ala Tyr Met Ala Pro
        200                 205                 210

GAG CGC ATC GAC CCT CCA GAT CCC ACC AAG CCT GAC TAT GAC ATC CGA      967
Glu Arg Ile Asp Pro Pro Asp Pro Thr Lys Pro Asp Tyr Asp Ile Arg
    215                 220                 225

GCT GAT GTG TGG AGC CTG GGC ATC TCA CTG GTG GAG CTG GCA ACA GGA     1015
Ala Asp Val Trp Ser Leu Gly Ile Ser Leu Val Glu Leu Ala Thr Gly
230                 235                 240                 245

CAG TTC CCC TAT AAG AAC TGC AAG ACG GAC TTT GAG GTC CTC ACC AAA     1063
Gln Phe Pro Tyr Lys Asn Cys Lys Thr Asp Phe Glu Val Leu Thr Lys
                250                 255                 260

GTC CTA CAG GAA GAG CCC CCA CTC CTG CCT GGT CAC ATG GGC TTC TCA     1111
Val Leu Gln Glu Glu Pro Pro Leu Leu Pro Gly His Met Gly Phe Ser
            265                 270                 275

GGG GAC TTC CAG TCA TTT GTC AAA GAC TGC CTT ACT AAA GAT CAC AGG     1159
Gly Asp Phe Gln Ser Phe Val Lys Asp Cys Leu Thr Lys Asp His Arg
        280                 285                 290

AAG AGA CCA AAG TAT AAT AAG CTA CTT GAA CAC AGC TTC ATC AAG CAC     1207
Lys Arg Pro Lys Tyr Asn Lys Leu Leu Glu His Ser Phe Ile Lys His
    295                 300                 305

TAT GAG ATA CTC GAG GTG GAT GTC GCG TCC TGG TTT AAG GAT GTC ATG     1255
Tyr Glu Ile Leu Glu Val Asp Val Ala Ser Trp Phe Lys Asp Val Met
310                 315                 320                 325
```

```
GCG AAG ACC GAG TCC CCA AGG ACT AGT GGA GTC CTG AGT CAG CAC CAT      1303
Ala Lys Thr Glu Ser Pro Arg Thr Ser Gly Val Leu Ser Gln His His
                330                 335                 340

CTG CCC TTC TTC AGG TAGCCTCATG GCAGCGGCCA GCCCCGCAGG GGCCCCGGGC C    1359
Leu Pro Phe Phe Arg
            345

ACGGCCACCG ACCCCCCCCC CAACCTGGCC AACCCAGCTG CCCATCAGGG GACCTGGGAC    1419
CTGGACGACT GCCAAGGACT GAGGACAGAA AGTAGGGGGT TCCCATCCAG CTCTGACTCC    1479
CTGCCTACCA GCTGTGGACA AAAGGGCATG CTGGTTCCTA ATCCCTCCCA CTCTGGGGTC    1539
AGCCAGCAGT GTGAGCCCCA TCCCACCCCG ACAGACACTG TGAACGGAAG ACAGCAGGCC    1599
AAAAAAAAAA AAAAAAAAAA AAAA                                           1623
```

(2) INFORMATION FOR SEQ ID NO:18:

(i) SEQUENCE CHARACTERISTICS:
(A) LENGTH: 346 amino acids
(B) TYPE: amino acid
(D) TOPOLOGY: linear

(ii) MOLECULE TYPE: protein

(v) FRAGMENT TYPE: internal

(xi) SEQUENCE DESCRIPTION: SEQ ID NO:18:

```
Met Leu Gly Leu Pro Ser Thr Leu Phe Thr Pro Arg Ser Met Glu Ser
 1               5                  10                  15
Ile Glu Ile Asp Gln Lys Leu Gln Glu Ile Met Lys Gln Thr Gly Tyr
            20                  25                  30
Leu Thr Ile Gly Gly Gln Arg Tyr Gln Ala Glu Ile Asn Asp Leu Glu
        35                  40                  45
Asn Leu Gly Glu Met Gly Ser Gly Thr Cys Gly Gln Val Trp Lys Met
    50                  55                  60
Arg Phe Arg Lys Thr Gly His Ile Ile Ala Val Lys Gln Met Arg Arg
65                  70                  75                  80
Ser Gly Asn Lys Glu Glu Asn Lys Arg Ile Leu Met Asp Leu Asp Val
                85                  90                  95
Val Leu Lys Ser His Asp Cys Pro Tyr Ile Val Gln Cys Phe Gly Thr
            100                 105                 110
Phe Ile Thr Asn Thr Asp Val Phe Ile Ala Met Glu Leu Met Gly Thr
        115                 120                 125
Cys Ala Glu Lys Leu Lys Lys Arg Met Gln Gly Pro Ile Pro Glu Arg
    130                 135                 140
Ile Leu Gly Asn Met Thr Val Ala Ile Val Lys Ala Leu Tyr Tyr Leu
145                 150                 155                 160
Lys Glu Lys His Gly Val Ile His Arg Asp Val Lys Pro Ser Asn Ile
                165                 170                 175
Leu Leu Asp Glu Arg Gly Gln Ile Lys Leu Cys Asp Phe Gly Ile Ser
            180                 185                 190
Gly Arg Leu Val Asp Ser Lys Ala Lys Thr Arg Ser Ala Gly Cys Ala
        195                 200                 205
Ala Tyr Met Ala Pro Glu Arg Ile Asp Pro Pro Asp Pro Thr Lys Pro
    210                 215                 220
Asp Tyr Asp Ile Arg Ala Asp Val Trp Ser Leu Gly Ile Ser Leu Val
225                 230                 235                 240
Glu Leu Ala Thr Gly Gln Phe Pro Tyr Lys Asn Cys Lys Thr Asp Phe
                245                 250                 255
Glu Val Leu Thr Lys Val Leu Gln Glu Glu Pro Pro Leu Leu Pro Gly
            260                 265                 270
His Met Gly Phe Ser Gly Asp Phe Gln Ser Phe Val Lys Asp Cys Leu
        275                 280                 285
Thr Lys Asp His Arg Lys Arg Pro Lys Tyr Asn Lys Leu Leu Glu His
    290                 295                 300
Ser Phe Ile Lys His Tyr Glu Ile Leu Glu Val Asp Val Ala Ser Trp
305                 310                 315                 320
```

```
Phe Lys Asp Val Met Ala Lys Thr Glu Ser Pro Arg Thr Ser Gly Val
                325                 330                 335
Leu Ser Gln His His Leu Pro Phe Phe Arg
            340                 345
```

(2) INFORMATION FOR SEQ ID NO:19:

(i) SEQUENCE CHARACTERISTICS:
(A) LENGTH: 1465 base pairs
(B) TYPE: nucleic acid
(C) STRANDEDNESS: double
(D) TOPOLOGY: linear

(ii) MOLECULE TYPE: cDNA

(ix) FEATURE:
(A) NAME/KEY: Coding Sequence
(B) LOCATION: 3...1169

(xi) SEQUENCE DESCRIPTION: SEQ ID NO:19:

```
GC ACG AGC CCT GCT CCT GCC CCG TCC CAG CGA GCA GCC CTG CAA CTC        47
   Thr Ser Pro Ala Pro Ala Pro Ser Gln Arg Ala Ala Leu Gln Leu
    1               5                  10                  15

CCA CTG GCC AAC GAT GGG GGC AGC CGC TCA CCA TCC TCA GAG AGC TCC       95
Pro Leu Ala Asn Asp Gly Gly Ser Arg Ser Pro Ser Ser Glu Ser Ser
                20                  25                  30

CCA CAG CAC CCT ACA CCC CCC ACC CGG CCC CGC CAC ATG CTG GGG CTC      143
Pro Gln His Pro Thr Pro Pro Thr Arg Pro Arg His Met Leu Gly Leu
            35                  40                  45

CCA TCA ACC TTG TTC ACA CCG CGC AGT ATG GAG AGC ATC GAG ATT GAC      191
Pro Ser Thr Leu Phe Thr Pro Arg Ser Met Glu Ser Ile Glu Ile Asp
        50                  55                  60

CAG AAG CTG CAG GAG ATC ATG AAG CAG ACA GGG TAC CTG ACT ATC GGG      239
Gln Lys Leu Gln Glu Ile Met Lys Gln Thr Gly Tyr Leu Thr Ile Gly
    65                  70                  75

GGC CAG CGT TAT CAG GCA GAA ATC AAT GAC TTG GAG AAC TTG GGT GAG      287
Gly Gln Arg Tyr Gln Ala Glu Ile Asn Asp Leu Glu Asn Leu Gly Glu
80                  85                  90                  95

ATG GGC AGT GGT ACC TGT GGT CAG GTG TGG AAG ATG CGG TTC CGG AAG      335
Met Gly Ser Gly Thr Cys Gly Gln Val Trp Lys Met Arg Phe Arg Lys
                100                 105                 110

ACA GGC CAC ATC ATT GCT GTT AAG CAA ATG CGG CGC TCT GGG AAC AAG      383
Thr Gly His Ile Ile Ala Val Lys Gln Met Arg Arg Ser Gly Asn Lys
            115                 120                 125

GAA GAG AAT AAG CGC ATT TTG ATG GAC CTG GAT GTA GTA CTC AAG AGC      431
Glu Glu Asn Lys Arg Ile Leu Met Asp Leu Asp Val Val Leu Lys Ser
        130                 135                 140

CAT GAC TGC CCT TAC ATC GTT CAG TGC TTT GGC ACC TTC ATC ACC AAC      479
His Asp Cys Pro Tyr Ile Val Gln Cys Phe Gly Thr Phe Ile Thr Asn
    145                 150                 155

ACA GAC GTC TTT ATT GCC ATG GAG CTC ATG GGC ACA TGT GCA GAG AAG      527
Thr Asp Val Phe Ile Ala Met Glu Leu Met Gly Thr Cys Ala Glu Lys
160                 165                 170                 175
```

```
CTG AAG AAA CGA ATG CAG GGC CCC ATT CCA GAG CGA ATC CTG GGC AAG      575
Leu Lys Lys Arg Met Gln Gly Pro Ile Pro Glu Arg Ile Leu Gly Lys
                180                 185                 190

ATG ACT GTG GCG ATT GTG AAA GCA CTG TAC TAT CTG AAG GAG AAG CAT      623
Met Thr Val Ala Ile Val Lys Ala Leu Tyr Tyr Leu Lys Glu Lys His
            195                 200                 205

GGC GTC ATC CAT CGC GAT GTC AAA CCC TCC AAC ATC CTG CTA GAT GAG      671
Gly Val Ile His Arg Asp Val Lys Pro Ser Asn Ile Leu Leu Asp Glu
        210                 215                 220

CGG GGC CAG ATC AAG CTC TGT GAC TTT GGC ATC AGT GGC CGC CTT GTT      719
Arg Gly Gln Ile Lys Leu Cys Asp Phe Gly Ile Ser Gly Arg Leu Val
    225                 230                 235

GAC TCC AAA GCC AAA ACA CGG AGT GCT GGC TGT GCT GCC TAT ATG GCT      767
Asp Ser Lys Ala Lys Thr Arg Ser Ala Gly Cys Ala Ala Tyr Met Ala
240                 245                 250                 255

CCC GAG CGC ATC GAC CCT CCA GAT CCC ACC AAG CCT GAC TAT GAC ATC      815
Pro Glu Arg Ile Asp Pro Pro Asp Pro Thr Lys Pro Asp Tyr Asp Ile
                260                 265                 270

CGA GCT GAT GTG TGG AGC CTG GGC ATC TCA CTG GTG GAG CTG GCA ACA      863
Arg Ala Asp Val Trp Ser Leu Gly Ile Ser Leu Val Glu Leu Ala Thr
            275                 280                 285

GGA CAG TTC CCC TAT AAG AAC TGC AAG ACG GAC TTT GAG GTC CTC ACC      911
Gly Gln Phe Pro Tyr Lys Asn Cys Lys Thr Asp Phe Glu Val Leu Thr
        290                 295                 300

AAA GTC CTA CAG GAA GAG CCC CCA CTC CTG CCT GGT CAC ATG GGC TTC      959
Lys Val Leu Gln Glu Glu Pro Pro Leu Leu Pro Gly His Met Gly Phe
    305                 310                 315

TCA GGG GAC TTC CAG TCA TTT GTC AAA GAC TGC CTT ACT AAA GAT CAC     1007
Ser Gly Asp Phe Gln Ser Phe Val Lys Asp Cys Leu Thr Lys Asp His
320                 325                 330                 335

AGG AAG AGA CCA AAG TAT AAT AAG CTA CTT GAA CAC AGC TTC ATC AAG     1055
Arg Lys Arg Pro Lys Tyr Asn Lys Leu Leu Glu His Ser Phe Ile Lys
                340                 345                 350

CAC TAT GAG ATA CTC GAG GTG GAT GTC GCG TCC TGG TTT AAG GAT GTC     1103
His Tyr Glu Ile Leu Glu Val Asp Val Ala Ser Trp Phe Lys Asp Val
            355                 360                 365

ATG GCG AAG ACC GAG TCC CCA AGG ACT AGT GGA GTC CTG AGT CAG CAC     1151
Met Ala Lys Thr Glu Ser Pro Arg Thr Ser Gly Val Leu Ser Gln His
        370                 375                 380

CAT CTG CCC TTC TTC AGG TAGCCTCATG GCAGCGGCCA GCCCCGCAGG GGCCCCGG   1207
His Leu Pro Phe Phe Arg
    385

GCCACGGCCA CCGACCCCCC CCCCAACCTG GCCAACCCAG CTGCCCATCA GGGGACCTGG   1267
GACCTGGACG ACTGCCAAGG ACTGAGGACA GAAAGTAGGG GGTTCCCATC CAGCTCTGAC   1327
TCCCTGCCTA CCAGCTGTGG ACAAAAGGGC ATGCTGGTTC CTAATCCCTC CCACTCTGGG   1387
GTCAGCCAGC AGTGTGAGCC CCATCCCACC CCGACAGACA CTGTGAACGG AAGACAGCAA   1447
AAAAAAAAAA AAAAAAAA                                                 1465
```

(2) INFORMATION FOR SEQ ID NO:20:

(i) SEQUENCE CHARACTERISTICS:
(A) LENGTH: 389 amino acids

(B) TYPE: amino acid
(D) TOPOLOGY: linear

(ii) MOLECULE TYPE: protein

(v) FRAGMENT TYPE: internal

(xi) SEQUENCE DESCRIPTION: SEQ ID NO:20:

```
Thr Ser Pro Ala Pro Ala Pro Ser Gln Arg Ala Ala Leu Gln Leu Pro
 1               5                  10                  15
Leu Ala Asn Asp Gly Gly Ser Arg Ser Pro Ser Ser Glu Ser Ser Pro
            20                  25                  30
Gln His Pro Thr Pro Pro Thr Arg Pro Arg His Met Leu Gly Leu Pro
        35                  40                  45
Ser Thr Leu Phe Thr Pro Arg Ser Met Glu Ser Ile Glu Ile Asp Gln
    50                  55                  60
Lys Leu Gln Glu Ile Met Lys Gln Thr Gly Tyr Leu Thr Ile Gly Gly
65                  70                  75                  80
Gln Arg Tyr Gln Ala Glu Ile Asn Asp Leu Glu Asn Leu Gly Glu Met
                85                  90                  95
Gly Ser Gly Thr Cys Gly Gln Val Trp Lys Met Arg Phe Arg Lys Thr
            100                 105                 110
Gly His Ile Ile Ala Val Lys Gln Met Arg Arg Ser Gly Asn Lys Glu
        115                 120                 125
Glu Asn Lys Arg Ile Leu Met Asp Leu Asp Val Val Leu Lys Ser His
    130                 135                 140
Asp Cys Pro Tyr Ile Val Gln Cys Phe Gly Thr Phe Ile Thr Asn Thr
145                 150                 155                 160
Asp Val Phe Ile Ala Met Glu Leu Met Gly Thr Cys Ala Glu Lys Leu
                165                 170                 175
Lys Lys Arg Met Gln Gly Pro Ile Pro Glu Arg Ile Leu Gly Lys Met
            180                 185                 190
Thr Val Ala Ile Val Lys Ala Leu Tyr Tyr Leu Lys Glu Lys His Gly
        195                 200                 205
Val Ile His Arg Asp Val Lys Pro Ser Asn Ile Leu Leu Asp Glu Arg
    210                 215                 220
Gly Gln Ile Lys Leu Cys Asp Phe Gly Ile Ser Gly Arg Leu Val Asp
225                 230                 235                 240
Ser Lys Ala Lys Thr Arg Ser Ala Gly Cys Ala Ala Tyr Met Ala Pro
                245                 250                 255
Glu Arg Ile Asp Pro Pro Asp Pro Thr Lys Pro Asp Tyr Asp Ile Arg
            260                 265                 270
Ala Asp Val Trp Ser Leu Gly Ile Ser Leu Val Glu Leu Ala Thr Gly
        275                 280                 285
Gln Phe Pro Tyr Lys Asn Cys Lys Thr Asp Phe Glu Val Leu Thr Lys
    290                 295                 300
Val Leu Gln Glu Glu Pro Pro Leu Leu Pro Gly His Met Gly Phe Ser
305                 310                 315                 320
Gly Asp Phe Gln Ser Phe Val Lys Asp Cys Leu Thr Lys Asp His Arg
                325                 330                 335
Lys Arg Pro Lys Tyr Asn Lys Leu Leu Glu His Ser Phe Ile Lys His
            340                 345                 350
Tyr Glu Ile Leu Glu Val Asp Val Ala Ser Trp Phe Lys Asp Val Met
        355                 360                 365
Ala Lys Thr Glu Ser Pro Arg Thr Ser Gly Val Leu Ser Gln His His
    370                 375                 380
Leu Pro Phe Phe Arg
385
```

(2) INFORMATION FOR SEQ ID NO:21:

(i) SEQUENCE CHARACTERISTICS:
(A) LENGTH: 393 amino acids
(B) TYPE: amino acid
(D) TOPOLOGY: linear

(ii) MOLECULE TYPE: protein

(xi) SEQUENCE DESCRIPTION: SEQ ID NO:21:

```
Ser Ala Ser Ser Ser Ser Ser Ser Ala Ser Ala Phe Ala Ser Ala Ala
 1               5                  10                  15
Pro Ala Thr Gly Thr Phe Gly Gly Thr Tyr Thr Pro Pro Thr Thr Arg
            20                  25                  30
Val Ser Arg Ala Thr Pro Thr Leu Pro Met Leu Ser Ser Gly Pro Gly
        35                  40                  45
Gly Gly Leu Asn Arg Thr Arg Pro Asn Ile Leu Pro Leu Pro Thr Pro
    50                  55                  60
Pro His Pro Pro Val Ser Glu Thr Asp Met Lys Leu Lys Ile Ile Met
65                  70                  75                  80
Glu Gln Thr Gly Lys Leu Asn Ile Asn Gly Arg Gln Tyr Pro Thr Asp
                85                  90                  95
Ile Asn Asp Leu Lys His Leu Gly Asp Leu Gly Asn Gly Thr Ser Gly
            100                 105                 110
Asn Val Val Lys Met Met His Leu Ser Ser Asn Thr Ile Ile Ala Val
        115                 120                 125
Lys Gln Met Arg Arg Thr Gly Asn Ala Glu Glu Asn Lys Arg Ile Leu
    130                 135                 140
Met Asp Leu Asp Val Val Leu Lys Ser His Asp Cys Lys Tyr Ile Val
145                 150                 155                 160
Lys Cys Leu Gly Cys Phe Val Arg Asp Pro Asp Val Trp Ile Cys Met
                165                 170                 175
Glu Leu Met Ser Met Cys Phe Asp Lys Leu Leu Lys Leu Ser Lys Lys
            180                 185                 190
Pro Val Pro Glu Gln Ile Leu Gly Lys Val Thr Val Ala Thr Val Asn
        195                 200                 205
Ala Leu Ser Tyr Leu Lys Asp Lys His Gly Val Ile His Arg Asp Val
    210                 215                 220
Lys Pro Ser Asn Ile Leu Ile Asp Glu Arg Gly Asn Ile Lys Leu Cys
225                 230                 235                 240
Asp Phe Gly Ile Ser Gly Arg Leu Val Asp Ser Lys Ala Lys Thr Arg
                245                 250                 255
Ser Ala Gly Cys Ala Ala Tyr Met Ala Pro Glu Arg Ile Asp Pro Lys
            260                 265                 270
Lys Pro Lys Tyr Asp Ile Arg Ala Asp Val Trp Ser Leu Gly Ile Thr
        275                 280                 285
Leu Val Glu Leu Ala Thr Ala Arg Ser Pro Tyr Glu Gly Cys Asn Thr
    290                 295                 300
Asp Phe Glu Val Leu Thr Lys Val Leu Asp Ser Glu Pro Pro Cys Leu
305                 310                 315                 320
Pro Tyr Gly Glu Gly Tyr Asn Phe Ser Gln Gln Phe Arg Asp Phe Val
                325                 330                 335
Ile Lys Cys Leu Thr Lys Asn His Gln Asp Arg Pro Lys Tyr Pro Glu
            340                 345                 350
Leu Leu Ala Gln Pro Phe Ile Arg Ile Tyr Glu Ser Ala Lys Val Asp
        355                 360                 365
Val Pro Asn Gln Ser Ile Lys Asp Asn Arg Leu Arg Ala Asn Gly Asp
    370                 375                 380
Pro Thr Leu Gln Arg Leu Pro Asn Ser
385                 390
```

(2) INFORMATION FOR SEQ ID NO:22:

(i) SEQUENCE CHARACTERISTICS:
(A) LENGTH: 405 amino acids
(B) TYPE: amino acid

(D) TOPOLOGY: linear

(ii) MOLECULE TYPE: protein

(xi) SEQUENCE DESCRIPTION: SEQ ID NO:22:

```
Ile Gly Gln Val Leu Pro Glu Ala Thr Thr Thr Ala Phe Glu Tyr Glu
 1               5                  10                  15
Asp Glu Asp Gly Asp Arg Ile Thr Val Arg Ser Asp Glu Glu Met Lys
            20                  25                  30
Ala Met Leu Ser Tyr Tyr Tyr Ser Thr Val Met Glu Gln Gln Val Asn
        35                  40                  45
Gly Gln Leu Ile Glu Pro Leu Gln Ile Phe Pro Arg Ala Cys Lys Pro
    50                  55                  60
Pro Gly Glu Arg Asn Ile His Gly Leu Lys Val Asn Thr Arg Ala Gly
65                  70                  75                  80
Pro Ser Gln His Ser Ser Pro Ala Val Ser Asp Ser Leu Pro Ser Asn
                85                  90                  95
Ser Leu Lys Lys Ser Ser Ala Glu Leu Lys Lys Ile Leu Ala Asn Gly
            100                 105                 110
Gln Met Asn Glu Gln Asp Ile Arg Tyr Arg Asp Thr Leu Gly His Gly
        115                 120                 125
Asn Gly Gly Thr Val Glu Lys Met Arg His Val Pro Ser Gly Lys Ile
    130                 135                 140
Leu Ala Val Lys Val Ile Leu Leu Asp Ile Thr Leu Glu Leu Gln Lys
145                 150                 155                 160
Gln Ile Met Ser Glu Leu Glu Ile Leu Ile Lys Cys Asp Ser Ser Tyr
                165                 170                 175
Ile Ile Gly Phe Tyr Gly Ala Phe Phe Val Glu Asn Arg Ile Ser Ile
            180                 185                 190
Cys Thr Glu Phe Met Asp Gly Gly Ser Leu Asp Asp Ile Gly Lys Met
        195                 200                 205
Pro Glu His Val Leu Gly Arg Ile Ala Val Ala Val Val Lys Gly Leu
    210                 215                 220
Thr Tyr Lys Gly Leu Thr Tyr Leu Trp Ser Leu Lys Ile Leu His Arg
225                 230                 235                 240
Asp Val Lys Pro Ser Asn Met Val Asn Thr Arg Gly Gln Val Lys Leu
                245                 250                 255
Cys Asp Phe Gly Val Ser Thr Gln Leu Val Asn Ser Ile Ala Lys Thr
            260                 265                 270
Tyr Val Gly Thr Asn Ala Tyr Met Ala Pro Glu Arg Ile Ser Gly Glu
        275                 280                 285
Gln Tyr Gly Ile His Ser Asp Val Trp Ser Leu Gly Ile Thr Met Ile
    290                 295                 300
Glu Leu Ala Thr Gly Arg Phe Pro Tyr Pro Lys Trp Asn Ser Val Leu
305                 310                 315                 320
Gln Leu Leu Gln Cys Ile Val Asp Glu Asp Ser Pro Val Leu Pro Val
                325                 330                 335
Gly Glu Phe Ser Glu Pro Phe Val His Phe Ile Thr Gln Cys Met Arg
            340                 345                 350
Thr Gln Pro Lys Glu Arg Pro Ala Pro Glu Glu Leu Met Gly His Pro
        355                 360                 365
Phe Ile Val Gln Phe Asn Asp Gly Asn Ala Ala Val Val Ser Met Trp
    370                 375                 380
Val Cys Arg Ala Leu Glu Glu Arg Arg Thr Ser Arg Gly Pro Arg Glu
385                 390                 395                 400
Ala Ala Ala Gly His
                405
```

(2) INFORMATION FOR SEQ ID NO:23:

(i) SEQUENCE CHARACTERISTICS:
(A) LENGTH: 18 base pairs
(B) TYPE: nucleic acid
(C) STRANDEDNESS: single
(D) TOPOLOGY: linear

(ii) MOLECULE TYPE: DNA

(xi) SEQUENCE DESCRIPTION: SEQ ID NO:23:

```
ATNGCNGTNA ARCARATG                                                    18
```

(2) INFORMATION FOR SEQ ID NO:24:

(i) SEQUENCE CHARACTERISTICS:
(A) LENGTH: 20 base pairs
(B) TYPE: nucleic acid
(C) STRANDEDNESS: single
(D) TOPOLOGY: linear

(ii) MOLECULE TYPE: DNA

(xi) SEQUENCE DESCRIPTION: SEQ ID NO:24:

```
ATNCKYTCNG GNGCCATRTA                                                  20
```

(2) INFORMATION FOR SEQ ID NO:25:

(i) SEQUENCE CHARACTERISTICS:
(A) LENGTH: 843 base pairs
(B) TYPE: nucleic acid
(C) STRANDEDNESS: double
(D) TOPOLOGY: linear

(ii) MOLECULE TYPE: cDNA

(ix) FEATURE:
(A) NAME/KEY: Coding Sequence
(B) LOCATION: 62...841

(xi) SEQUENCE DESCRIPTION: SEQ ID NO:25:

```
TGTTTGTCTG CCGGACTGAC GGGCGGCCGG GCGGTGCGCG GCGGCGGTGG CGGCGGGGAA      60
G ATG GCG GCG TCC TCC CTG GAA CAG AAG CTG TCC CGC CTG GAA GCA AAG     109
  Met Ala Ala Ser Ser Leu Glu Gln Lys Leu Ser Arg Leu Glu Ala Lys
   1               5                  10                  15

CTG AAG CAG GAG AAC CGG GAG GCC CGG CGG AGG ATC GAC CTC AAC CTG       157
Leu Lys Gln Glu Asn Arg Glu Ala Arg Arg Arg Ile Asp Leu Asn Leu
            20                  25                  30

GAT ATC AGC CCC CAG CGG CCC AGG CCC ACC CTG CAG CTC CCG CTG GCC       205
Asp Ile Ser Pro Gln Arg Pro Arg Pro Thr Leu Gln Leu Pro Leu Ala
        35                  40                  45

AAC GAT GGG GGC AGC CGC TCG CCA TCC TCA GAG AGC TCC CCG CAG CAC       253
Asn Asp Gly Gly Ser Arg Ser Pro Ser Ser Glu Ser Ser Pro Gln His
    50                  55                  60

CCC ACG CCC CCC GCC CGG CCC CGC CAC ATG CTG GGG CTC CCG TCA ACC       301
Pro Thr Pro Pro Ala Arg Pro Arg His Met Leu Gly Leu Pro Ser Thr
65                  70                  75                  80

CTG TTC ACA CCC CGC AGC ATG GAG AGC ATT GAG ATT GAC CAG AAG CTG       349
Leu Phe Thr Pro Arg Ser Met Glu Ser Ile Glu Ile Asp Gln Lys Leu
                85                  90                  95

CAG GAG ATC ATG AAG CAG ACG GGC TAC CTG ACC ATC GGG GGC CAG CGC       397
Gln Glu Ile Met Lys Gln Thr Gly Tyr Leu Thr Ile Gly Gly Gln Arg
            100                 105                 110

TAC CAG GCA GAA ATC AAC GAC CTG GAG AAC TTG GGC GAG ATG GGC AGC       445
Tyr Gln Ala Glu Ile Asn Asp Leu Glu Asn Leu Gly Glu Met Gly Ser
        115                 120                 125
```

```
GGC ACC TGC GGC CAG GTG TGG AAG ATG CGC TTC CGG AAG ACC GGC CAC      493
Gly Thr Cys Gly Gln Val Trp Lys Met Arg Phe Arg Lys Thr Gly His
    130                 135                 140

GTC ATT GCC GTT AAG CAA ATG CGG CGC TCC GGG AAC AAG GAG GAG AAC      541
Val Ile Ala Val Lys Gln Met Arg Arg Ser Gly Asn Lys Glu Glu Asn
145                 150                 155                 160

AAG CGC ATC CTC ATG GAC CTG GAT GTG GTG CTG AAG AGC CAC GAC TGC      589
Lys Arg Ile Leu Met Asp Leu Asp Val Val Leu Lys Ser His Asp Cys
                165                 170                 175

CCC TAC ATC GTG CAG TGC TTT GGG ACG TTC ATC ACC AAC ACG GAC GTC      637
Pro Tyr Ile Val Gln Cys Phe Gly Thr Phe Ile Thr Asn Thr Asp Val
            180                 185                 190

TTC ATC GCC ATG GAG CTC ATG GGC ACC TGC GCT GAG AAG CTC AAG AAG      685
Phe Ile Ala Met Glu Leu Met Gly Thr Cys Ala Glu Lys Leu Lys Lys
        195                 200                 205

CGG ATG CAG GGC CCC ATC CCC GAG CGC ATT CTG GGC AAG ATG ACA GTG      733
Arg Met Gln Gly Pro Ile Pro Glu Arg Ile Leu Gly Lys Met Thr Val
    210                 215                 220

GCG ATT GTG AAG GCG CTG TAC TAC CTG AAG GAG AAG CAC GGT GTC ATC      781
Ala Ile Val Lys Ala Leu Tyr Tyr Leu Lys Glu Lys His Gly Val Ile
225                 230                 235                 240

CAC CGC GAC GTC AAG CCC TCC AAC ATC CTG CTG GAC GAG CGG GGC CAG      829
His Arg Asp Val Lys Pro Ser Asn Ile Leu Leu Asp Glu Arg Gly Gln
                245                 250                 255

ATC AAG CTG TGC GA                                                   843
Ile Lys Leu Cys
            260
```

(2) INFORMATION FOR SEQ ID NO:26:

(i) SEQUENCE CHARACTERISTICS:
(A) LENGTH: 260 amino acids
(B) TYPE: amino acid
(D) TOPOLOGY: linear

(ii) MOLECULE TYPE: protein

(v) FRAGMENT TYPE: internal

(xi) SEQUENCE DESCRIPTION: SEQ ID NO:26:

```
Met Ala Ala Ser Ser Leu Glu Gln Lys Leu Ser Arg Leu Glu Ala Lys
 1               5                  10                  15
Leu Lys Gln Glu Asn Arg Glu Ala Arg Arg Arg Ile Asp Leu Asn Leu
            20                  25                  30
Asp Ile Ser Pro Gln Arg Pro Arg Pro Thr Leu Gln Leu Pro Leu Ala
        35                  40                  45
Asn Asp Gly Gly Ser Arg Ser Pro Ser Ser Glu Ser Ser Pro Gln His
    50                  55                  60
Pro Thr Pro Pro Ala Arg Pro Arg His Met Leu Gly Leu Pro Ser Thr
65                  70                  75                  80
Leu Phe Thr Pro Arg Ser Met Glu Ser Ile Glu Ile Asp Gln Lys Leu
                85                  90                  95
Gln Glu Ile Met Lys Gln Thr Gly Tyr Leu Thr Ile Gly Gly Gln Arg
            100                 105                 110
Tyr Gln Ala Glu Ile Asn Asp Leu Glu Asn Leu Gly Glu Met Gly Ser
        115                 120                 125
Gly Thr Cys Gly Gln Val Trp Lys Met Arg Phe Arg Lys Thr Gly His
    130                 135                 140
```

```
Val Ile Ala Val Lys Gln Met Arg Arg Ser Gly Asn Lys Glu Glu Asn
145                 150                 155                 160
Lys Arg Ile Leu Met Asp Leu Asp Val Val Leu Lys Ser His Asp Cys
                165                 170                 175
Pro Tyr Ile Val Gln Cys Phe Gly Thr Phe Ile Thr Asn Thr Asp Val
            180                 185                 190
Phe Ile Ala Met Glu Leu Met Gly Thr Cys Ala Glu Lys Leu Lys Lys
        195                 200                 205
Arg Met Gln Gly Pro Ile Pro Glu Arg Ile Leu Gly Lys Met Thr Val
    210                 215                 220
Ala Ile Val Lys Ala Leu Tyr Tyr Leu Lys Glu Lys His Gly Val Ile
225                 230                 235                 240
His Arg Asp Val Lys Pro Ser Asn Ile Leu Leu Asp Glu Arg Gly Gln
                245                 250                 255
Ile Lys Leu Cys
            260
```

(2) INFORMATION FOR SEQ ID NO:27:

(i) SEQUENCE CHARACTERISTICS:
(A) LENGTH: 1643 base pairs
(B) TYPE: nucleic acid
(C) STRANDEDNESS: double
(D) TOPOLOGY: linear

(ii) MOLECULE TYPE: cDNA

(ix) FEATURE:
(A) NAME/KEY: Coding Sequence
(B) LOCATION: 82...1338

(xi) SEQUENCE DESCRIPTION: SEQ ID NO:27:

```
AGCGCAGGCG CAGTGCGGTG TTTGTCTACC CCGGACTGAC GGGTGGCCTG GCGGTGAGCG      60
GCGGCAGCGG CGGCGGGGAA G ATG GCG GCG TCC TCC CTG GAG CAG AAG CTG       111
                        Met Ala Ala Ser Ser Leu Glu Gln Lys Leu
                         1               5                  10

TCC CGC CTG GAA GCC AAG CTG AAG CAG GAG AAC CGT GAG GCC CGC AGG       159
Ser Arg Leu Glu Ala Lys Leu Lys Gln Glu Asn Arg Glu Ala Arg Arg
            15                  20                  25

AGG ATC GAC CTC AAC TTG GAT ATC AGC CCA CAG CGG CCC AGG CCC ACC       207
Arg Ile Asp Leu Asn Leu Asp Ile Ser Pro Gln Arg Pro Arg Pro Thr
            30                  35                  40

CTG CAA CTC CCA CTG GCC AAC GAT GGG GGC AGC CGC TCA CCA TCC TCA       255
Leu Gln Leu Pro Leu Ala Asn Asp Gly Gly Ser Arg Ser Pro Ser Ser
        45                  50                  55

GAG AGC TCC CCA CAG CAC CCT ACA CCC CCC ACC CGG CCC CGC CAC ATG       303
Glu Ser Ser Pro Gln His Pro Thr Pro Pro Thr Arg Pro Arg His Met
    60                  65                  70

CTG GGG CTC CCA TCA ACC TTG TTC ACA CCG CGC AGT ATG GAG AGC ATC       351
Leu Gly Leu Pro Ser Thr Leu Phe Thr Pro Arg Ser Met Glu Ser Ile
75                  80                  85                  90

GAG ATT GAC CAG AAG CTG CAG GAG ATC ATG AAG CAG ACA GGG TAC CTG       399
Glu Ile Asp Gln Lys Leu Gln Glu Ile Met Lys Gln Thr Gly Tyr Leu
                95                 100                 105

ACT ATC GGG GGC CAG CGT TAT CAG GCA GAA ATC AAT GAC TTG GAG AAC       447
Thr Ile Gly Gly Gln Arg Tyr Gln Ala Glu Ile Asn Asp Leu Glu Asn
            110                 115                 120
```

```
TTG GGT GAG ATG GGC AGT GGT ACC TGT GGT CAG GTG TGG AAG ATG CGG      495
Leu Gly Glu Met Gly Ser Gly Thr Cys Gly Gln Val Trp Lys Met Arg
        125                 130                 135

TTC CGG AAG ACA GGC CAC ATC ATT GCT GTT AAG CAA ATG CGG CGC TCT      543
Phe Arg Lys Thr Gly His Ile Ile Ala Val Lys Gln Met Arg Arg Ser
    140                 145                 150

GGG AAC AAG GAA GAG AAT AAG CGC ATT TTG ATG GAC CTG GAT GTA GTA      591
Gly Asn Lys Glu Glu Asn Lys Arg Ile Leu Met Asp Leu Asp Val Val
155                 160                 165                 170

CTC AAG AGC CAT GAC TGC CCT TAC ATC GTT CAG TGC TTT GGC ACC TTC      639
Leu Lys Ser His Asp Cys Pro Tyr Ile Val Gln Cys Phe Gly Thr Phe
                175                 180                 185

ATC ACC AAC ACA GAC GTC TTT ATT GCC ATG GAG CTC ATG GGC ACA TGT      687
Ile Thr Asn Thr Asp Val Phe Ile Ala Met Glu Leu Met Gly Thr Cys
            190                 195                 200

GCA GAG AAG CTG AAG AAA CGA ATG CAG GGC CCC ATT CCA GAG CGA ATC      735
Ala Glu Lys Leu Lys Lys Arg Met Gln Gly Pro Ile Pro Glu Arg Ile
        205                 210                 215

CTG GGC AAG ATG ACT GTG GCG ATT GTG AAA GCA CTG TAC TAT CTG AAG      783
Leu Gly Lys Met Thr Val Ala Ile Val Lys Ala Leu Tyr Tyr Leu Lys
    220                 225                 230

GAG AAG CAT GGC GTC ATC CAT CGC GAT GTC AAA CCC TCC AAC ATC CTG      831
Glu Lys His Gly Val Ile His Arg Asp Val Lys Pro Ser Asn Ile Leu
235                 240                 245                 250

CTA GAT GAG CGG GGC CAG ATC AAG CTC TGT GAC TTT GGC ATC AGT GGC      879
Leu Asp Glu Arg Gly Gln Ile Lys Leu Cys Asp Phe Gly Ile Ser Gly
                255                 260                 265

CGC CTT GTT GAC TCC AAA GCC AAA ACA CGG AGT GCT GGC TGT GCT GCC      927
Arg Leu Val Asp Ser Lys Ala Lys Thr Arg Ser Ala Gly Cys Ala Ala
            270                 275                 280

TAT ATG GCT CCC GAG CGC ATC GAC CCT CCA GAT CCC ACC AAG CCT GAC      975
Tyr Met Ala Pro Glu Arg Ile Asp Pro Pro Asp Pro Thr Lys Pro Asp
        285                 290                 295

TAT GAC ATC CGA GCT GAT GTG TGG AGC CTG GGC ATC TCA CTG GTG GAG     1023
Tyr Asp Ile Arg Ala Asp Val Trp Ser Leu Gly Ile Ser Leu Val Glu
    300                 305                 310

CTG GCA ACA GGA CAG TTC CCC TAT AAG AAC TGC AAG ACG GAC TTT GAG     1071
Leu Ala Thr Gly Gln Phe Pro Tyr Lys Asn Cys Lys Thr Asp Phe Glu
315                 320                 325                 330

GTC CTC ACC AAA GTC CTA CAG GAA GAG CCC CCA CTC CTG CCT GGT CAC     1119
Val Leu Thr Lys Val Leu Gln Glu Glu Pro Pro Leu Leu Pro Gly His
                335                 340                 345

ATG GGC TTC TCA GGG GAC TTC CAG TCA TTT GTC AAA GAC TGC CTT ACT     1167
Met Gly Phe Ser Gly Asp Phe Gln Ser Phe Val Lys Asp Cys Leu Thr
            350                 355                 360

AAA GAT CAC AGG AAG AGA CCA AAG TAT AAT AAG CTA CTT GAA CAC AGC     1215
Lys Asp His Arg Lys Arg Pro Lys Tyr Asn Lys Leu Leu Glu His Ser
        365                 370                 375
```

TTC ATC AAG CAC TAT GAG ATA CTC GAG GTG GAT GTC GCG TCC TGG TTT 1263
Phe Ile Lys His Tyr Glu Ile Leu Glu Val Asp Val Ala Ser Trp Phe
380 385 390

AAG GAT GTC ATG GCG AAG ACC GAG TCC CCA AGG ACT AGT GGA GTC CTG 1311
Lys Asp Val Met Ala Lys Thr Glu Ser Pro Arg Thr Ser Gly Val Leu
395 400 405 410

AGT CAG CAC CAT CTG CCC TTC TTC AGG TAGCCTCATG GCAGCGGCCA GCCCCGC 1365
Ser Gln His His Leu Pro Phe Phe Arg
415

AGGGGCCCCG GGCCACGGCC ACCGACCCCC CCCCCAACCT GGCCAACCCA GCTGCCCATC 1425
AGGGGACCTG GGACCTGGAC GACTGCCAAG GACTGAGGAC AGAAAGTAGG GGGTTCCCAT 1485
CCAGCTCTGA CTCCCTGCCT ACCAGCTGTG GACAAAAGGG CATGCTGGTT CCTAATCCCT 1545
CCCACTCTGG GGTCAGCCAG CAGTGTGAGC CCCATCCCAC CCCGACAGAC ACTGTGAACG 1605
GAAGACAGCA GGCCAAAAAA AAAAAAAAAA AAAAAAAA 1643

(2) INFORMATION FOR SEQ ID NO:28:

(i) SEQUENCE CHARACTERISTICS:
(A) LENGTH: 419 amino acids
(B) TYPE: amino acid
(D) TOPOLOGY: linear

(ii) MOLECULE TYPE: protein

(v) FRAGMENT TYPE: internal

(xi) SEQUENCE DESCRIPTION: SEQ ID NO:28:

Met Ala Ala Ser Ser Leu Glu Gln Lys Leu Ser Arg Leu Glu Ala Lys
1 5 10 15
Leu Lys Gln Glu Asn Arg Glu Ala Arg Arg Arg Ile Asp Leu Asn Leu
20 25 30
Asp Ile Ser Pro Gln Arg Pro Arg Pro Thr Leu Gln Leu Pro Leu Ala
35 40 45
Asn Asp Gly Gly Ser Arg Ser Pro Ser Ser Glu Ser Ser Pro Gln His
50 55 60
Pro Thr Pro Pro Thr Arg Pro Arg His Met Leu Gly Leu Pro Ser Thr
65 70 75 80
Leu Phe Thr Pro Arg Ser Met Glu Ser Ile Glu Ile Asp Gln Lys Leu
85 90 95
Gln Glu Ile Met Lys Gln Thr Gly Tyr Leu Thr Ile Gly Gly Gln Arg
100 105 110
Tyr Gln Ala Glu Ile Asn Asp Leu Glu Asn Leu Gly Glu Met Gly Ser
115 120 125
Gly Thr Cys Gly Gln Val Trp Lys Met Arg Phe Arg Lys Thr Gly His
130 135 140
Ile Ile Ala Val Lys Gln Met Arg Arg Ser Gly Asn Lys Glu Glu Asn
145 150 155 160
Lys Arg Ile Leu Met Asp Leu Asp Val Val Leu Lys Ser His Asp Cys
165 170 175
Pro Tyr Ile Val Gln Cys Phe Gly Thr Phe Ile Thr Asn Thr Asp Val
180 185 190
Phe Ile Ala Met Glu Leu Met Gly Thr Cys Ala Glu Lys Leu Lys Lys
195 200 205
Arg Met Gln Gly Pro Ile Pro Glu Arg Ile Leu Gly Lys Met Thr Val
210 215 220
Ala Ile Val Lys Ala Leu Tyr Tyr Leu Lys Glu Lys His Gly Val Ile
225 230 235 240
His Arg Asp Val Lys Pro Ser Asn Ile Leu Leu Asp Glu Arg Gly Gln
245 250 255
Ile Lys Leu Cys Asp Phe Gly Ile Ser Gly Arg Leu Val Asp Ser Lys
260 265 270
Ala Lys Thr Arg Ser Ala Gly Cys Ala Ala Tyr Met Ala Pro Glu Arg
275 280 285

```
Ile Asp Pro Pro Asp Pro Thr Lys Pro Asp Tyr Asp Ile Arg Ala Asp
    290                 295                 300
Val Trp Ser Leu Gly Ile Ser Leu Val Glu Leu Ala Thr Gly Gln Phe
305                 310                 315                 320
Pro Tyr Lys Asn Cys Lys Thr Asp Phe Glu Val Leu Thr Lys Val Leu
                325                 330                 335
Gln Glu Glu Pro Pro Leu Leu Pro Gly His Met Gly Phe Ser Gly Asp
            340                 345                 350
Phe Gln Ser Phe Val Lys Asp Cys Leu Thr Lys Asp His Arg Lys Arg
        355                 360                 365
Pro Lys Tyr Asn Lys Leu Leu Glu His Ser Phe Ile Lys His Tyr Glu
    370                 375                 380
Ile Leu Glu Val Asp Val Ala Ser Trp Phe Lys Asp Val Met Ala Lys
385                 390                 395                 400
Thr Glu Ser Pro Arg Thr Ser Gly Val Leu Ser Gln His His Leu Pro
                405                 410                 415
Phe Phe Arg
```

(2) INFORMATION FOR SEQ ID NO:29:

(i) SEQUENCE CHARACTERISTICS:
(A) LENGTH: 1578 base pairs
(B) TYPE: nucleic acid
(C) STRANDEDNESS: double
(D) TOPOLOGY: linear

(ii) MOLECULE TYPE: cDNA

(ix) FEATURE:
(A) NAME/KEY: Coding Sequence
(B) LOCATION: 281...1420

(xi) SEQUENCE DESCRIPTION: SEQ ID NO:29:

```
GGAAAGGCAG CCTCCTGTAG GTGAAAATTC TGTTCACTAC CTGGCCACCT GGCCTGACTG    60
ACCTTCACAG CTTGATCATC TTCCTGAAGA GGCATTCAGG ATTCCCTCCA TCCCTACCCC   120
TTCTGGACAA AGTCTTCCAC GTTTCCTTCC TGGGAGTTTC TTCCAGGAAC TGGAGATACC   180
CAGAGCCCTG CAACTCCCAC TGGCCAACGA TGGGGGCAGC CGCTCACCAT CCTCAGAGAG   240
CTCCCCACAG CACCCTACAC CCCCCACCCG GCCCCGCCAC  ATG CTG GGG CTC CCA   295
                                             Met Leu Gly Leu Pro
                                              1               5

TCA ACC TTG TTC ACA CCG CGC AGT ATG GAG AGC ATC GAG ATT GAC CAG   343
Ser Thr Leu Phe Thr Pro Arg Ser Met Glu Ser Ile Glu Ile Asp Gln
                10                  15                  20

AAG CTG CAG GAG ATC ATG AAG CAG ACA GGG TAC CTG ACT ATC GGG GGC   391
Lys Leu Gln Glu Ile Met Lys Gln Thr Gly Tyr Leu Thr Ile Gly Gly
            25                  30                  35

CAG CGT TAT CAG GCA GAA ATC AAT GAC TTG GAG AAC TTG GGT GAG ATG   439
Gln Arg Tyr Gln Ala Glu Ile Asn Asp Leu Glu Asn Leu Gly Glu Met
        40                  45                  50

GGC AGT GGT ACC TGT GGT CAG GTG TGG AAG ATG CGG TTC CGG AAG ACA   487
Gly Ser Gly Thr Cys Gly Gln Val Trp Lys Met Arg Phe Arg Lys Thr
    55                  60                  65

GGC CAC ATC ATT GCT GTT AAG CAA ATG CGG CGC TCT GGG AAC AAG GAA   535
Gly His Ile Ile Ala Val Lys Gln Met Arg Arg Ser Gly Asn Lys Glu
70                  75                  80                  85

GAG AAT AAG CGC ATT TTG ATG GAC CTG GAT GTA GTA CTC AAG AGC CAT   583
Glu Asn Lys Arg Ile Leu Met Asp Leu Asp Val Val Leu Lys Ser His
                90                  95                  100
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```
GAC TGC CCT TAC ATC GTT CAG TGC TTT GGC ACC TTC ATC ACC AAC ACA        631
Asp Cys Pro Tyr Ile Val Gln Cys Phe Gly Thr Phe Ile Thr Asn Thr
            105                 110                 115

GAC GTC TTT ATT GCC ATG GAG CTC ATG GGC ACA TGT GCA GAG AAG CTG        679
Asp Val Phe Ile Ala Met Glu Leu Met Gly Thr Cys Ala Glu Lys Leu
        120                 125                 130

AAG AAA CGA ATG CAG GGC CCC ATT CCA GAG CGA ATC CTG GGC AAG ATG        727
Lys Lys Arg Met Gln Gly Pro Ile Pro Glu Arg Ile Leu Gly Lys Met
    135                 140                 145

ACT GTG GCG ATT GTG AAA GCA CTG TAC TAT CTG AAG GAG AAG CAT GGC        775
Thr Val Ala Ile Val Lys Ala Leu Tyr Tyr Leu Lys Glu Lys His Gly
150                 155                 160                 165

GTC ATC CAT CGC GAT GTC AAA CCC TCC AAC ATC CTG CTA GAT GAG CGG        823
Val Ile His Arg Asp Val Lys Pro Ser Asn Ile Leu Leu Asp Glu Arg
                170                 175                 180

GGC CAG ATC AAG CTC TGT GAC TTT GGC ATC AGT GGC CGC CTT GTT GAC        871
Gly Gln Ile Lys Leu Cys Asp Phe Gly Ile Ser Gly Arg Leu Val Asp
            185                 190                 195

TCC AAA GCC AAA ACA CGG AGT GCT GGC TGT GCT GCC TAT ATG GCT CCC        919
Ser Lys Ala Lys Thr Arg Ser Ala Gly Cys Ala Ala Tyr Met Ala Pro
        200                 205                 210

GAG CGC ATC GAC CCT CCA GAT CCC ACC AAG CCT GAC TAT GAC ATC CGA        967
Glu Arg Ile Asp Pro Pro Asp Pro Thr Lys Pro Asp Tyr Asp Ile Arg
    215                 220                 225

GCT GAT GTG TGG AGC CTG GGC ATC TCA CTG GTG GAG CTG GCA ACA GGA       1015
Ala Asp Val Trp Ser Leu Gly Ile Ser Leu Val Glu Leu Ala Thr Gly
230                 235                 240                 245

CAG TTC CCC TAT AAG AAC TGC AAG ACG GAC TTT GAG GTC CTC ACC AAA       1063
Gln Phe Pro Tyr Lys Asn Cys Lys Thr Asp Phe Glu Val Leu Thr Lys
                250                 255                 260

GTC CTA CAG GAA GAG CCC CCA CTC CTG CCT GGT CAC ATG GGC TTC TCA       1111
Val Leu Gln Glu Glu Pro Pro Leu Leu Pro Gly His Met Gly Phe Ser
            265                 270                 275

GGG GAC TTC CAG TCA TTT GTC AAA GAC TGC CTT ACT AAA GAT CAC AGG       1159
Gly Asp Phe Gln Ser Phe Val Lys Asp Cys Leu Thr Lys Asp His Arg
        280                 285                 290

AAG AGA CCA AAG TAT AAT AAG CTA CTT GAA CAC AGC TTC ATC ATC AAG       1207
Lys Arg Pro Lys Tyr Asn Lys Leu Leu Glu His Ser Phe Ile Ile Lys
    295                 300                 305

CAC TAT GAG ATA CTC GAG GTG GAT GTC GCG TCC TGG TTT AAG GAT GTC       1255
His Tyr Glu Ile Leu Glu Val Asp Val Ala Ser Trp Phe Lys Asp Val
310                 315                 320                 325

ATG GCG AAG ACC GAG TCC CCA AGG ACT AGT GGA GTC CTG AGT CAG CAC       1303
Met Ala Lys Thr Glu Ser Pro Arg Thr Ser Gly Val Leu Ser Gln His
                330                 335                 340

CAT CTG CCC TTC TTC AGT GGG AGT CTG GAG GAG TCT CCC ACT TCC CCA       1351
His Leu Pro Phe Phe Ser Gly Ser Leu Glu Glu Ser Pro Thr Ser Pro
            345                 350                 355

CCT TCT CCC AAG TCC TTC CCT CTG TCA CCA GCC ATC CCT CAG GCC CAG       1399
Pro Ser Pro Lys Ser Phe Pro Leu Ser Pro Ala Ile Pro Gln Ala Gln
        360                 365                 370
```

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GCA GAG TGG GTC TCG GGC AGG TAGGGACCTG GAGTGGCCTG GTCCCACCCT CTGA     1454
Ala Glu Trp Val Ser Gly Arg
    375                 380

CCTCCTCCTC AGGCCACCAG TGTTGCCCTC TTCCCTTTTT AAAACAAAAT ACCCTTGTTT     1514
GTAAATCCTT AGACGCTTGA GAATAAAACC CTTCCCTTTT CTTCCGAAAA AAAAAAAAAA     1574
AAAA                                                                  1578
```

(2) INFORMATION FOR SEQ ID NO:30:

(i) SEQUENCE CHARACTERISTICS:
(A) LENGTH: 380 amino acids
(B) TYPE: amino acid
(D) TOPOLOGY: linear

(ii) MOLECULE TYPE: protein

(v) FRAGMENT TYPE: internal

(xi) SEQUENCE DESCRIPTION: SEQ ID NO:30:

```
Met Leu Gly Leu Pro Ser Thr Leu Phe Thr Pro Arg Ser Met Glu Ser
 1               5                  10                  15
Ile Glu Ile Asp Gln Lys Leu Gln Glu Ile Met Lys Gln Thr Gly Tyr
            20                  25                  30
Leu Thr Ile Gly Gly Gln Arg Tyr Gln Ala Glu Ile Asn Asp Leu Glu
        35                  40                  45
Asn Leu Gly Glu Met Gly Ser Gly Thr Cys Gly Gln Val Trp Lys Met
    50                  55                  60
Arg Phe Arg Lys Thr Gly His Ile Ile Ala Val Lys Gln Met Arg Arg
65                  70                  75                  80
Ser Gly Asn Lys Glu Glu Asn Lys Arg Ile Leu Met Asp Leu Asp Val
                85                  90                  95
Val Leu Lys Ser His Asp Cys Pro Tyr Ile Val Gln Cys Phe Gly Thr
            100                 105                 110
Phe Ile Thr Asn Thr Asp Val Phe Ile Ala Met Glu Leu Met Gly Thr
        115                 120                 125
Cys Ala Glu Lys Leu Lys Lys Arg Met Gln Gly Pro Ile Pro Glu Arg
    130                 135                 140
Ile Leu Gly Lys Met Thr Val Ala Ile Val Lys Ala Leu Tyr Tyr Leu
145                 150                 155                 160
Lys Glu Lys His Gly Val Ile His Arg Asp Val Lys Pro Ser Asn Ile
                165                 170                 175
Leu Leu Asp Glu Arg Gly Gln Ile Lys Leu Cys Asp Phe Gly Ile Ser
            180                 185                 190
Gly Arg Leu Val Asp Ser Lys Ala Lys Thr Arg Ser Ala Gly Cys Ala
        195                 200                 205
Ala Tyr Met Ala Pro Glu Arg Ile Asp Pro Pro Asp Pro Thr Lys Pro
    210                 215                 220
Asp Tyr Asp Ile Arg Ala Asp Val Trp Ser Leu Gly Ile Ser Leu Val
225                 230                 235                 240
Glu Leu Ala Thr Gly Gln Phe Pro Tyr Lys Asn Cys Lys Thr Asp Phe
                245                 250                 255
Glu Val Leu Thr Lys Val Leu Gln Glu Glu Pro Pro Leu Leu Pro Gly
            260                 265                 270
His Met Gly Phe Ser Gly Asp Phe Gln Ser Phe Val Lys Asp Cys Leu
        275                 280                 285
Thr Lys Asp His Arg Lys Arg Pro Lys Tyr Asn Lys Leu Leu Glu His
    290                 295                 300
Ser Phe Ile Ile Lys His Tyr Glu Ile Leu Glu Val Asp Val Ala Ser
305                 310                 315                 320
Trp Phe Lys Asp Val Met Ala Lys Thr Glu Ser Pro Arg Thr Ser Gly
                325                 330                 335
Val Leu Ser Gln His His Leu Pro Phe Phe Ser Gly Ser Leu Glu Glu
            340                 345                 350
```

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Ser Pro Thr Ser Pro Pro Ser Pro Lys Ser Phe Pro Leu Ser Pro Ala
        355                 360                 365
Ile Pro Gln Ala Gln Ala Glu Trp Val Ser Gly Arg
    370                 375                 380
```

(2) INFORMATION FOR SEQ ID NO:31:

(i) SEQUENCE CHARACTERISTICS:
(A) LENGTH: 1598 base pairs
(B) TYPE: nucleic acid
(C) STRANDEDNESS: double
(D) TOPOLOGY: linear

(ii) MOLECULE TYPE: cDNA

(ix) FEATURE:
(A) NAME/KEY: Coding Sequence
(B) LOCATION: 82...1440

(xi) SEQUENCE DESCRIPTION: SEQ ID NO:31:

```
AGCGCAGGCG CAGTGCGGTG TTTGTCTACC CCGGACTGAC GGGTGGCCTG GCGGTGAGCG      60
GCGGCAGCGG CGGCGGGGAA G ATG GCG GCG TCC TCC CTG GAG CAG AAG CTG       111
                        Met Ala Ala Ser Ser Leu Glu Gln Lys Leu
                         1               5                  10

TCC CGC CTG GAA GCC AAG CTG AAG CAG GAG AAC CGT GAG GCC CGC AGG       159
Ser Arg Leu Glu Ala Lys Leu Lys Gln Glu Asn Arg Glu Ala Arg Arg
                15                  20                  25

AGG ATC GAC CTC AAC TTG GAT ATC AGC CCA CAG CGG CCC AGG CCC ACC       207
Arg Ile Asp Leu Asn Leu Asp Ile Ser Pro Gln Arg Pro Arg Pro Thr
            30                  35                  40

CTG CAA CTC CCA CTG GCC AAC GAT GGG GGC AGC CGC TCA CCA TCC TCA       255
Leu Gln Leu Pro Leu Ala Asn Asp Gly Gly Ser Arg Ser Pro Ser Ser
        45                  50                  55

GAG AGC TCC CCA CAG CAC CCT ACA CCC CCC ACC CGG CCC CGC CAC ATG       303
Glu Ser Ser Pro Gln His Pro Thr Pro Pro Thr Arg Pro Arg His Met
    60                  65                  70

CTG GGG CTC CCA TCA ACC TTG TTC ACA CCG CGC AGT ATG GAG AGC ATC       351
Leu Gly Leu Pro Ser Thr Leu Phe Thr Pro Arg Ser Met Glu Ser Ile
 75                  80                  85                  90

GAG ATT GAC CAG AAG CTG CAG GAG ATC ATG AAG CAG ACA GGG TAC CTG       399
Glu Ile Asp Gln Lys Leu Gln Glu Ile Met Lys Gln Thr Gly Tyr Leu
                95                 100                 105

ACT ATC GGG GGC CAG CGT TAT CAG GCA GAA ATC AAT GAC TTG GAG AAC       447
Thr Ile Gly Gly Gln Arg Tyr Gln Ala Glu Ile Asn Asp Leu Glu Asn
            110                 115                 120

TTG GGT GAG ATG GGC AGT GGT ACC TGT GGT CAG GTG TGG AAG ATG CGG       495
Leu Gly Glu Met Gly Ser Gly Thr Cys Gly Gln Val Trp Lys Met Arg
        125                 130                 135

TTC CGG AAG ACA GGC CAC ATC ATT GCT GTT AAG CAA ATG CGG CGC TCT       543
Phe Arg Lys Thr Gly His Ile Ile Ala Val Lys Gln Met Arg Arg Ser
    140                 145                 150

GGG AAC AAG GAA GAG AAT AAG CGC ATT TTG ATG GAC CTG GAT GTA GTA       591
Gly Asn Lys Glu Glu Asn Lys Arg Ile Leu Met Asp Leu Asp Val Val
155                 160                 165                 170
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```
CTC AAG AGC CAT GAC TGC CCT TAC ATC GTT CAG TGC TTT GGC ACC TTC      639
Leu Lys Ser His Asp Cys Pro Tyr Ile Val Gln Cys Phe Gly Thr Phe
                175                 180                 185

ATC ACC AAC ACA GAC GTC TTT ATT GCC ATG GAG CTC ATG GGC ACA TGT      687
Ile Thr Asn Thr Asp Val Phe Ile Ala Met Glu Leu Met Gly Thr Cys
            190                 195                 200

GCA GAG AAG CTG AAG AAA CGA ATG CAG GGC CCC ATT CCA GAG CGA ATC      735
Ala Glu Lys Leu Lys Lys Arg Met Gln Gly Pro Ile Pro Glu Arg Ile
        205                 210                 215

CTG GGC AAG ATG ACT GTG GCG ATT GTG AAA GCA CTG TAC TAT CTG AAG      783
Leu Gly Lys Met Thr Val Ala Ile Val Lys Ala Leu Tyr Tyr Leu Lys
    220                 225                 230

GAG AAG CAT GGC GTC ATC CAT CGC GAT GTC AAA CCC TCC AAC ATC CTG      831
Glu Lys His Gly Val Ile His Arg Asp Val Lys Pro Ser Asn Ile Leu
235                 240                 245                 250

CTA GAT GAG CGG GGC CAG ATC AAG CTC TGT GAC TTT GGC ATC AGT GGC      879
Leu Asp Glu Arg Gly Gln Ile Lys Leu Cys Asp Phe Gly Ile Ser Gly
                255                 260                 265

CGC CTT GTT GAC TCC AAA GCC AAA ACA CGG AGT GCT GGC TGT GCT GCC      927
Arg Leu Val Asp Ser Lys Ala Lys Thr Arg Ser Ala Gly Cys Ala Ala
            270                 275                 280

TAT ATG GCT CCC GAG CGC ATC GAC CCT CCA GAT CCC ACC AAG CCT GAC      975
Tyr Met Ala Pro Glu Arg Ile Asp Pro Pro Asp Pro Thr Lys Pro Asp
        285                 290                 295

TAT GAC ATC CGA GCT GAT GTG TGG AGC CTG GGC ATC TCA CTG GTG GAG     1023
Tyr Asp Ile Arg Ala Asp Val Trp Ser Leu Gly Ile Ser Leu Val Glu
    300                 305                 310

CTG GCA ACA GGA CAG TTC CCC TAT AAG AAC TGC AAG ACG GAC TTT GAG     1071
Leu Ala Thr Gly Gln Phe Pro Tyr Lys Asn Cys Lys Thr Asp Phe Glu
315                 320                 325                 330

GTC CTC ACC AAA GTC CTA CAG GAA GAG CCC CCA CTC CTG CCT GGT CAC     1119
Val Leu Thr Lys Val Leu Gln Glu Glu Pro Pro Leu Leu Pro Gly His
                335                 340                 345

ATG GGC TTC TCA GGG GAC TTC CAG TCA TTT GTC AAA GAC TGC CTT ACT     1167
Met Gly Phe Ser Gly Asp Phe Gln Ser Phe Val Lys Asp Cys Leu Thr
            350                 355                 360

AAA GAT CAC AGG AAG AGA CCA AAG TAT AAT AAG CTA CTT GAA CAC AGC     1215
Lys Asp His Arg Lys Arg Pro Lys Tyr Asn Lys Leu Leu Glu His Ser
        365                 370                 375

TTC ATC ATC AAG CAC TAT GAG ATA CTC GAG GTG GAT GTC GCG TCC TGG     1263
Phe Ile Ile Lys His Tyr Glu Ile Leu Glu Val Asp Val Ala Ser Trp
    380                 385                 390

TTT AAG GAT GTC ATG GCG AAG ACC GAG TCC CCA AGG ACT AGT GGA GTC     1311
Phe Lys Asp Val Met Ala Lys Thr Glu Ser Pro Arg Thr Ser Gly Val
395                 400                 405                 410

CTG AGT CAG CAC CAT CTG CCC TTC TTC AGT GGG AGT CTG GAG GAG TCT     1359
Leu Ser Gln His His Leu Pro Phe Phe Ser Gly Ser Leu Glu Glu Ser
                415                 420                 425

CCC ACT TCC CCA CCT TCT CCC AAG TCC TTC CCT CTG TCA CCA GCC ATC     1407
Pro Thr Ser Pro Pro Ser Pro Lys Ser Phe Pro Leu Ser Pro Ala Ile
            430                 435                 440
```

```
CCT CAG GCC CAG GCA GAG TGG GTC TCG GGC AGG TAGGGACCTG GAGTGGCCTG   1460
Pro Gln Ala Gln Ala Glu Trp Val Ser Gly Arg
        445                 450

GTCCCACCCT CTGACCTCCT CCTCAGGCCA CCAGTGTTGC CCTCTTCCCT TTTTAAAACA   1520
AAATACCCTT GTTTGTAAAT CCTTAGACGC TTGAGAATAA AACCCTTCCC TTTTCTTCCG   1580
AAAAAAAAAA AAAAAAAA                                                 1598
```

(2) INFORMATION FOR SEQ ID NO:32:

(i) SEQUENCE CHARACTERISTICS:
(A) LENGTH: 453 amino acids
(B) TYPE: amino acid
(D) TOPOLOGY: linear

(ii) MOLECULE TYPE: protein

(v) FRAGMENT TYPE: internal

(xi) SEQUENCE DESCRIPTION: SEQ ID NO:32:

```
Met Ala Ala Ser Ser Leu Glu Gln Lys Leu Ser Arg Leu Glu Ala Lys
 1               5                  10                  15
Leu Lys Gln Glu Asn Arg Glu Ala Arg Arg Arg Ile Asp Leu Asn Leu
            20                  25                  30
Asp Ile Ser Pro Gln Arg Pro Arg Pro Thr Leu Gln Leu Pro Leu Ala
        35                  40                  45
Asn Asp Gly Gly Ser Arg Ser Pro Ser Ser Glu Ser Ser Pro Gln His
    50                  55                  60
Pro Thr Pro Pro Thr Arg Pro Arg His Met Leu Gly Leu Pro Ser Thr
65                  70                  75                  80
Leu Phe Thr Pro Arg Ser Met Glu Ser Ile Glu Ile Asp Gln Lys Leu
                85                  90                  95
Gln Glu Ile Met Lys Gln Thr Gly Tyr Leu Thr Ile Gly Gly Gln Arg
            100                 105                 110
Tyr Gln Ala Glu Ile Asn Asp Leu Glu Asn Leu Gly Glu Met Gly Ser
        115                 120                 125
Gly Thr Cys Gly Gln Val Trp Lys Met Arg Phe Arg Lys Thr Gly His
    130                 135                 140
Ile Ile Ala Val Lys Gln Met Arg Arg Ser Gly Asn Lys Glu Glu Asn
145                 150                 155                 160
Lys Arg Ile Leu Met Asp Leu Asp Val Val Leu Lys Ser His Asp Cys
                165                 170                 175
Pro Tyr Ile Val Gln Cys Phe Gly Thr Phe Ile Thr Asn Thr Asp Val
            180                 185                 190
Phe Ile Ala Met Glu Leu Met Gly Thr Cys Ala Glu Lys Leu Lys Lys
        195                 200                 205
Arg Met Gln Gly Pro Ile Pro Glu Arg Ile Leu Gly Lys Met Thr Val
    210                 215                 220
Ala Ile Val Lys Ala Leu Tyr Tyr Leu Lys Glu Lys His Gly Val Ile
225                 230                 235                 240
His Arg Asp Val Lys Pro Ser Asn Ile Leu Leu Asp Glu Arg Gly Gln
                245                 250                 255
Ile Lys Leu Cys Asp Phe Gly Ile Ser Gly Arg Leu Val Asp Ser Lys
            260                 265                 270
Ala Lys Thr Arg Ser Ala Gly Cys Ala Ala Tyr Met Ala Pro Glu Arg
        275                 280                 285
Ile Asp Pro Pro Asp Pro Thr Lys Pro Asp Tyr Asp Ile Arg Ala Asp
    290                 295                 300
Val Trp Ser Leu Gly Ile Ser Leu Val Glu Leu Ala Thr Gly Gln Phe
305                 310                 315                 320
Pro Tyr Lys Asn Cys Lys Thr Asp Phe Glu Val Leu Thr Lys Val Leu
                325                 330                 335
Gln Glu Glu Pro Pro Leu Leu Pro Gly His Met Gly Phe Ser Gly Asp
            340                 345                 350
```

```
Phe Gln Ser Phe Val Lys Asp Cys Leu Thr Lys Asp His Arg Lys Arg
        355                 360                 365
Pro Lys Tyr Asn Lys Leu Leu Glu His Ser Phe Ile Ile Lys His Tyr
    370                 375                 380
Glu Ile Leu Glu Val Asp Val Ala Ser Trp Phe Lys Asp Val Met Ala
385                 390                 395                     400
Lys Thr Glu Ser Pro Arg Thr Ser Gly Val Leu Ser Gln His His Leu
                405                 410                 415
Pro Phe Phe Ser Gly Ser Leu Glu Glu Ser Pro Thr Ser Pro Pro Ser
            420                 425                 430
Pro Lys Ser Phe Pro Leu Ser Pro Ala Ile Pro Gln Ala Gln Ala Glu
        435                 440                 445
Trp Val Ser Gly Arg
    450
```

(2) INFORMATION FOR SEQ ID NO:33:

(i) SEQUENCE CHARACTERISTICS:
(A) LENGTH: 44 amino acids
(B) TYPE: amino acid
(D) TOPOLOGY: linear

(ii) MOLECULE TYPE: protein

(xi) SEQUENCE DESCRIPTION: SEQ ID NO:33:

```
Met Xaa Ser Pro Ala Pro Ala Pro Ser Gln Arg Ala Ala Leu Gln Leu
 1               5                  10                  15
Pro Leu Ala Asn Asp Gly Gly Ser Arg Ser Pro Ser Ser Glu Ser Ser
            20                  25                  30
Pro Gln His Pro Thr Pro Pro Thr Arg Pro Arg His
        35                  40
```

(2) INFORMATION FOR SEQ ID NO:34:

(i) SEQUENCE CHARACTERISTICS:
(A) LENGTH: 77 amino acids
(B) TYPE: amino acid
(D) TOPOLOGY: linear

(ii) MOLECULE TYPE: protein

(xi) SEQUENCE DESCRIPTION: SEQ ID NO:34:

```
Glu Gly Gly Gly Val Lys His Met Ala Lys Leu Tyr Val Phe Tyr Gly
 1               5                  10                  15
Ala Gly Cys Met Glu Met Ser Asp Ile Glu Leu Leu Leu His Arg Asp
            20                  25                  30
Lys Pro Asn Leu Gly Lys Cys Asp Phe Gly Ser Gly Leu Ser Ala Gly
        35                  40                  45
Tyr Met Pro Glu Arg Tyr Val Ser Asp Trp Ser Gly Glu Ala Arg Pro
    50                  55                  60
Phe Leu Val Pro Leu Phe Phe Cys Leu Lys Arg Leu His
65                  70                  75
```

INTERNATIONAL SEARCH REPORT

International application No.
PCT/US98/14101

A. CLASSIFICATION OF SUBJECT MATTER
IPC(6) :C07H 21/04
US CL :536/23.5; 435/183
According to International Patent Classification (IPC) or to both national classification and IPC

B. FIELDS SEARCHED
Minimum documentation searched (classification system followed by classification symbols)
U.S. : 536/23.5; 435/4, 183

Documentation searched other than minimum documentation to the extent that such documents are included in the fields searched

Electronic data base consulted during the international search (name of data base and, where practicable, search terms used)
Please See Extra Sheet.

C. DOCUMENTS CONSIDERED TO BE RELEVANT

Category*	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
A,P	CUENDA, A. et al., "Differential activation of stress-activated protein kinase kinases SKK4/MKK7 and SKK1/MKK4 by the mixed-lineage kinase-2 and mitogen-activated protein kinase kinase(MKK) kinase-1," Biochemical Journal, 01 July 1998, Volume 333, part 1, pages 11-15; see entire document.	1,2, 10-12
A	MOODIE, S.A. et al., "Complexes of Ras-GTP with Raf-1 and Mitogen-Activated Protein Kinase Kinase," Science, 11 June 1993, volume 260, pages 1658-1661, see pages 1658-1659.	1, 2, 10-12

[X] Further documents are listed in the continuation of Box C. [ ] See patent family annex.

* Special categories of cited documents:
"A" document defining the general state of the art which is not considered to be of particular relevance
"E" earlier document published on or after the international filing date
"L" document which may throw doubts on priority claim(s) or which is cited to establish the publication date of another citation or other special reason (as specified)
"O" document referring to an oral disclosure, use, exhibition or other means
"P" document published prior to the international filing date but later than the priority date claimed
"T" later document published after the international filing date or priority date and not in conflict with the application but cited to understand the principle or theory underlying the invention
"X" document of particular relevance; the claimed invention cannot be considered novel or cannot be considered to involve an inventive step when the document is taken alone
"Y" document of particular relevance; the claimed invention cannot be considered to involve an inventive step when the document is combined with one or more other such documents, such combination being obvious to a person skilled in the art
"&" document member of the same patent family

Date of the actual completion of the international search
24 SEPTEMBER 1998

Date of mailing of the international search report
29 . 10 . 1998

Name and mailing address of the ISA/US
Commissioner of Patents and Trademarks
Box PCT
Washington, D.C. 20231
Facsimile No. (703) 305-3230

Authorized officer
BRADLEY L. SISSON
Telephone No. (703) 308-0196

C (Continuation). DOCUMENTS CONSIDERED TO BE RELEVANT

Category*	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
Y	DENT, P. et al., "Activation of Mitogen-Activated Protein Kinase Kinase by v-Raf in NIH 3T3 Cells and in Vitro," Science, 04 September 1992, volume 257, pages 1404-1407, see pages 1404-1406.	1, 2
A	IRIE, K. et al., "MKK1 and MKK2, Which Encode Saccharomyces cervisiae Mitogen-Activated Protein Kinase-Kinase Homologs, Function in the Pathway Mediated by Protein Kinase C," Molecular and Cellular Biology, May 1993, Vol. 13, No. 5, pages 3076-3083, see pages 3076-3081.	1, 2
Y	TRAVERSE, S. et al., "Sustained activation of the mitogen-activated protein (MAP) kinase cascade may be requried for differentiation of PC12 cells," Biochem. J. 1992, vol. 288, pages 351-355, see entire document.	1, 2
X, P	TOURNIER, C. et al., "Mitogen-activated protein kinase kinase 7 is an activator of the c-Jun NH(sub)2-terminal kinase," Proceedings of the National Academy of Sciences, July 1997, Vol. 94, pages 7337-7342; see entie document.	1, 2, 10-12
X, T	US 5,804,427 A (DAVIS et al.) 08 September 1998, see entire document.	1, 2, 10-12
A, P	US 5,753,446 A (JOHNSON) 19 May 1998, see entire document.	1, 2

B. FIELDS SEARCHED
Electronic data bases consulted (Name of data base and where practicable terms used):

APS; STN (file: Biosis, Registry)

Search Terms: mitogen activated protein kinase kinase; SEQ ID NO: 18, 20, 26, 28, 30, and 32

BOX II. OBSERVATIONS WHERE UNITY OF INVENTION WAS LACKING
This ISA found multiple inventions as follows:

This application contains the following inventions or groups of inventions which are not so linked as to form a single inventive concept under PCT Rule 13.1. In order for all inventions to be searched, the appropriate additional search fees must be paid.

Group I, claim(s)1 and 2, draawn to mammalian mitogen-activated protein kinase kinase (MKK); and claims 10-12, drawn to method of measuring the activity of a mitogen-activated protein kinase kinase (MKK7).

Group II, claim(s) 3-5, drawn to isolated polynucleotide encoding MKK; claim 6, drawn torecombinant expression vector; and claim 7, drawn to a host cell.

Group III, claim(s) 8 and 9, drawn to purified antibodies; and claim 13, drawn to an immuno-based method for measuring the synthesis of MKK7.

Group IV, claim(s)14, drawn to nucleic acid-based method for measuring the synthesis of MKK7.

Group V, claim(s) 15-17, drawn to a method for identifying a reagent that moduates MKK7 activity; claims 18 and 19, drawn to a method for identifying a reagent that modulates MKK7 synthesis; and claim 20, drawn to a nucleic acid-based method for identifying a reagent that modulates MKK7 expression.

Group VI, claim(s) 21-24, drawn to a method of treating a MKK7-mediated disorder.

The inventions listed as Groups I-VI do not relate to a single inventive concept under PCT Rule 13.1 because, under PCT Rule 13.2, they lack the same or corresponding special technical features for the following reasons: The invention of Group I is drawn to an enzyme and a related emthod of use while the invnetion of Group II is drawn to a nucleic acid, a recombinant

vector, and a life form- a host cell. Further, the invention of Group VI is drawn to a method of treating patients that may suffer from ischemic heart disease, kidney failure,oxidative liver damage, respiratory distress syndrome, heat radiation burns, etc., whereinsaid method requires the use of a drug. Said drug, however, is not the enzyme of Group I nor the nucleic acid, vector, or host cell of Group II. Further, the aspect of mitogen activated kinase kinase contributing to such diseases is known in the prior art. Accordingly, the claimed invnetions are not so inked by a special technical feature so to form a single inventive concept under PCT Rule 13.1.